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Results of the Health Effects Assessment for the Fourth Six-Year Review of Existing Chemical and Radionuclide National Primary Drinking Water Standards

Prepared by:

U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
Washington, DC 20460

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Disclaimer

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Acronyms and Abbreviations

AChE	Acetylcholinesterase
ADAF	Age dependent adjustment factors
ADD	Acceptable daily dose
ADI	Acceptable daily intake
AFC	Antibody forming cells
ALP	Alkaline phosphatase
AMA	American Medical Association
ATSDR	Agency for Toxic Substances and Disease Registry
BAT	Best available technologies
BMCL	Benchmark concentration lower confidence limit
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMR	Benchmark response
BW	Body weight
CalEPA	California Environmental Protection Agency
CARC	Cancer Assessment Review Committee
CASRN	Chemical Abstract Service Registry Number
CBI	Confidential business information
CSF	Cancer slope factor
CSFII	Continuing Survey of Food Intake by Individuals
DBCP	1,2-Dibromo-3-chloropropane
DEHA	Di(2-ethylhexyl)adipate
DEHP	Di(2-ethylhexyl)phthalate
DTXSID	Distributed Structure-Searchable Toxicity substance identifier
DW	Drinking water
DWEL	Drinking water equivalent value
DWI	Drinking water intake
DWSHA	Drinking Water Standards and Health Advisory
EDB	Ethylene dibromide
EFH	Exposure Factors Handbook
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FMC	FMC Corporation
FQPA	Food Quality Protection Act
GDWQ	Guidelines for Drinking Water Quality
HA	Health Advisory
HBV	Health-based value
HC	Health Canada
HCB	Hexachlorobenzene
HECD	Health and Ecological Criteria Division
HED	Human equivalent dose
HHS	Human Health Services
IARC	International Agency for Research on Cancer
IOM	Institute of Occupational Medicine
IPCS	International Programme on Chemical Safety
IRDC	International Research and Development Corporation
IRIS	Integrated Risk Information System

JBRC	Japan Bioassay Research Center
JISA	Japanese Industrial Safety Association
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LCRI	Lead and Copper Rule Improvements
LCRR	Lead and Copper Rule Revisions
LH	Luteinizing hormone
LOAEL	Lowest-observed-adverse-effect level
MAC	Maximum acceptable concentration
MassDEP	Massachusetts Department of Environmental Protection
MCL	Maximum contaminant level
MCLG	Maximum contaminant level goals
MF	Modifying factor
MOA	Mode of action
MOE	Margin of exposure
MRL	Minimal risk level
NAS	National Academy of Medicine
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin lymphoma
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NPDWR	National Primary Drinking Water Regulations
NTP	National Toxicology Program
OAR	Office of Air and Radiation
OGWDW	Office of Groundwater and Drinking Water
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OW	Office of Water
PAD	Population-adjusted dose
PAH	Polycyclic Aromatic Hydrocarbon
PBPK	Physiologically-based pharmacokinetic
PCB	Polychlorinated biphenyl
PCE	Tetrachloroethylene
PCP	Pentachlorophenol
PERC	Perchloroethylene
PHG	Public Health Goal
PHS	Public Health Service
POD	Point of departure
PPRTV	Provisional Peer-Reviewed Toxicity Values
PQL	Practical Quantitation Limit
PTDI	Provisional tolerable daily intake
RBC	Red blood cell
RCC	Renal cell cancer
RED	Reregistration Eligibility Decision
RfC	Reference concentration
RfD	Reference dose
RfV	Reference value
RSC	Relative source contribution
SD	Standard deviation
SDWA	Safe Drinking Water Act

SMCL	Secondary maximum contaminant level
SWTR	Surface Water Treatment Rule
SYR	Six-Year Review
TAD	Total absorbed dose
TCDD	Tetrachlorodibenzo-p-dioxin
TCE	Trichloroethylene
TCT	Total chlorotriazines
TDI	Tolerable daily intake
TSCA	Toxic Substances Control Act
TVM	Tunica vaginalis mesotheliomas
TWA	Time-weighted average
UF	Uncertainty factor
UF_A	Animal to human (interspecies) UF
UF_D	Completeness of database UF
UF_H	Human to sensitive human (intraspecies) UF
UF_L	LOAEL to NOAEL UF
UF_S	Subchronic to Chronic UF
UL	Upper level
WHO	World Health Organization
WoS	Web of Science™

1 Introduction

The 1996 amendments to the Safe Drinking Water Act (SDWA), Section 1412(b)(9), require the U.S. Environmental Protection Agency (EPA) to review existing National Primary Drinking Water Regulations (NPDWRs) every six years and determine which, if any, are appropriate for revision. The SDWA Amendments also specify that any revision of an NPDWR will maintain or provide for greater protection of public health. The goal of the cyclical review is to determine whether it is appropriate to consider changes (i.e., to "list as a candidate for revision") to existing NPDWRs based on updated health effects and/or analytical or technological feasibility that have occurred since the regulations were promulgated.

In response to this mandate, EPA developed a Protocol for the Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2002a, 1263985; U.S. EPA, 2003a, 1263971} based on recommendations of the National Drinking Water Advisory Council (NDWAC) {U.S. EPA, 2000a, 10721409} and input from stakeholders representing a wide variety of interest groups. EPA subsequently updated this protocol {U.S. EPA, 2016a, 10721410; U.S. EPA, 2024a, 11346388} including for the fourth review effort. The protocol outlines the approach used to review and identify NPDWRs that may warrant revision. The key elements that are considered in the review process are health effects, analytical methods, occurrence and exposure, treatment technology, and other regulatory provisions (e.g., monitoring and reporting requirements).

The primary purpose of this document is to summarize the results of the review of the health effects component of the Six-Year Review 4 (SYR 4) effort for the chemical and radiological NPDWRs regulated under the Phase Rules and Radionuclides Rule. Seven NPDWRs fall under the disinfectants and disinfection byproducts rules (bromate, chloramine (as Cl_2), chlorine (as Cl_2), chlorine dioxide, chlorite, total trihalomethanes and haloacetic acids). These contaminants were not included in SYR 4 due to ongoing efforts to revise the Microbial and Disinfection Byproducts rules, following the Six-Year Review 3 (SYR 3) {U.S. EPA, 2022a, 10721416}.

Finally, two microbial contaminant groups (*Cryptosporidium* and viruses) are analyzed under the Ground Water Rule (GWR) as described in the Six-Year Review 4 Technical Support Document for Microbial Contaminant Regulations {U.S. EPA, 2024b, 11346389}. Microbial contaminants regulated under the surface water rules (i.e., Surface Water Treatment Rule (SWTR), Interim Enhanced SWTR LT1/LT2 Enhanced SWTR) were not reviewed in detail during SYR 4 because those rules were nominated as candidates for revision in SYR 3, and EPA is continuing to evaluate these contaminants for potential regulatory revisions {U.S. EPA, 2017a, 5638481}.

2 Scope of Six-Year Review 4

EPA has completed the health effects review for the fourth Six-Year Review (referred to here as "Six-Year Review 4;" SYR 4). EPA identified two chemical contaminants (lead and copper) with NPDWRs that were being considered as part of a recently completed action, and which are also currently part of an ongoing or pending regulatory action. EPA promulgated the Lead and Copper Rule Revisions (LCRR) on January 15, 2021 {U.S. EPA, 2021a, 11347324}. Subsequently, EPA reviewed the LCRR and announced the development of a proposed NPDWR: Lead and Copper Rule Improvements (LCRI) {U.S. EPA, 2021b, 11347325}. Information about the proposed LCRI can be found on the Office of Water (OW), Office of Groundwater and Drinking Water's (OGWDW's) LCRI webpage at https://www.epa.gov/ground-water-and-drinking-water/lead-and-copper-rule-improvements. In addition, nine chemicals (see List A, Table 2-1) were subject to an ongoing EPA health effects assessment or were nominated for an EPA health assessment. Therefore, additional health effects review as part of SYR 4 was not necessary for these chemicals. Information on the status of arsenic, chromium (total), copper, ethylbenzene, mercury, polychlorinated biphenyls (PCBs), and uranium can be found on Office of Research and Development's (ORD's) Integrated Risk Information System (IRIS) Program Outlook website at https://www.epa.gov/iris/iris-program-outlook.

Additional information about the EPA's Office of Air and Radiation (OAR) efforts to update the cancer risk coefficients and risk models for exposure to radionuclides through ingestion of water and about the status of the scientific review of the draft document titled "Federal Guidance Report No. 16: Cancer Risk Coefficients for Environmental Exposure to Radionuclides" can be found in the Federal Register {U.S. EPA, 2022b, 11346090} or at https://sab.epa.gov/ords/sab/r/sab_apex/sab_bkup/advisoryactivitydetail?p18_id=2616&clear=18&session=8694491614209.

Table 2-1. List A Chemicals—Health Effects Assessment in Process or Nominated for Health Assessment

Chemical	Existing MCLG (mg/L)	Status Under Six-Year Review 4
Alpha particles	0 pCi/L	Ongoing review conducted by EPA/OAR
Arsenic	0	Included in the IRIS Program Outlook as of 02/2023
Beta particles and photon emitters	0 millirems per year	Ongoing review conducted by EPA/OAR
Chromium (total)	0.1	Chromium VI included in the IRIS Program Outlook as of 02/2023
Ethylbenzene	0.7	Included in the IRIS Program Outlook as of 02/2023
Mercury	0.002	Included in the IRIS Program Outlook as of 02/2023
PCBs	0	Included in the IRIS Program Outlook as of 02/2023
Radium 226 and 228	0 pCi/L	Ongoing review conducted by EPA/OAR
Uranium	0	Included in the IRIS Program Outlook as of 02/2023

The following 62 contaminants (List B, Table 2-2) underwent a more detailed review including the evaluation of health effects information and risk-based values from publications by authoritative agencies. Thirteen of these contaminants are currently regulated under the Toxic Substances Control Act (TSCA). An additional 10 of these contaminants are concurrently regulated under broad authority granted in two major statutes, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food,

Drug, and Cosmetic Act (FFDCA)[1]. After the completion of the SYR 4 health assessment search step, OW became aware that EPA had previously cancelled the pesticide registration of alachlor and carbofuran {U.S. EPA, 2016b, 11328266; U.S. EPA, 2008a, 10494332}. Therefore, alachlor and carbofuran were inadvertently considered actively registered pesticides. This document summarizes the results of the review of the health effects component of the SYR 4 effort for the 62 contaminants identified below.

Table 2-2. List B Contaminants—Evaluated for Health Effects to Determine Potential Impact on the MCLG

1,1,1-Trichloroethane[1]	Endothall[2]
1,1,2-Trichloroethane	Endrin[3]
1,1-Dichloroethylene	Epichlorohydrin
1,2,4-Trichlorobenzene	Ethylene dibromide (EDB)[1]
1,2-Dibromo-3-chloropropane (DBCP)[3]	Fluoride
1,2-Dichloroethane[1]	Glyphosate[2]
1,2-Dichloropropane[1]	Heptachlor[3]
2,4 Dichlorophenoxy-acetic acid (2,4-D)[2]	Heptachlor epoxide[3]
Acrylamide	Hexachlorobenzene (HCB)
Alachlor[2]	Hexachlorocyclopentadiene
Antimony	Lindane[3]
Asbestos (fiber > 10 micrometers)[1]	Methoxychlor[3]
Atrazine[2]	Nitrate (as N)
Barium	Nitrite (as N)
Benzene	o-Dichlorobenzene (1,2-Dichlorobenzene)[1]
Benzo(a)pyrene	Oxamyl[2]
Beryllium	p-Dichlorobenzene (1,4-Dichlorobenzene)[1]
Cadmium	Pentachlorophenol (PCP)
Carbofuran[2]	Picloram[2]
Carbon tetrachloride[1]	Selenium
Chlordane[3]	Silvex (2,4,5-TP)[3]
Chlorobenzene	Simazine[2]
cis-1,2-Dichloroethylene	Styrene
Cyanide	Tetrachloroethylene (PCE)[1]
Dalapon[3]	Thallium
Di(2-ethylhexyl)adipate (DEHA)	Toluene
Di(2-ethylhexyl)phthalate (DEHP)[1]	Toxaphene[3]
Dichloromethane[1]	trans-1,2-Dichloroethylene[1]
Dinoseb[3]	Trichloroethylene (TCE)[1]
Dioxin (2,3,7,8-TCDD)	Vinyl chloride
Diquat[2]	Xylenes (total)

Notes:
[1] Contaminant concurrently regulated under TSCA.
[2] Actively registered pesticide: pesticide chemicals with active U.S. registrations and subject to EPA's registration review process under FIFRA.
[3] Pesticide not actively registered (previously labeled "cancelled pesticides"): pesticide chemicals with no active U.S. registrations and, therefore, not subject to EPA's registration review process under FIFRA.

2.1 Objectives and Report Organization

The first objective of SYR 4 was to identify new quantitative and/or qualitative health information from peer-reviewed health assessments that might support a change to the existing MCLG. For the SYR 4

[1] These laws were amended by the Food Quality Protection Act (FQPA) and the Pesticide Registration Improvement Act (PRIA).

health effects support document, the term "health assessment" is defined as a document that presents one or more toxicity values (see Section 3.1.1) and/or a cancer descriptor (see Section 3.1.2). Examples of names for health assessments from EPA include, but are not limited to, IRIS Toxicological Profiles, Office of Pollution Prevention and Toxics (OPPT) Risk Evaluations, and Office of Pesticide Programs (OPP) Human Health Risk Assessments (HHRAs). Health assessments produced from sources other than EPA include other specific names (e.g., California Environmental Protection Agency (CalEPA) Public Health Goal (PHG), Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile In the chemical summaries (Section 6), the specific name of the health assessment from each source is provided.

The second objective was to conduct a comprehensive search of the peer-reviewed health effects literature to identify potential emerging issues and to characterize data gaps. In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of chemical specific health effects and to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Section 3 provides background information on the Six-Year Review process including how EPA sets the MCLG for non-carcinogenic and carcinogenic contaminants.

Section 4 describes the methodologies used in SYR 4 including:

- identification and selection of human health toxicity assessments (Section 4.1),
- application of updated exposure factors {U.S. EPA, 2019, 7267482} to calculate a potential MCLG in SYR 4 (Section 4.2), and
- literature search strategies (Section 4.3).

Section 5 summarizes the findings for List B contaminants.

Section 6 includes individual contaminant summaries that provide the basis for the current MCLGs, health assessment identification and selection, derivation of potential MCLGs, and literature search results. Each summary concludes with an evaluation of the available health effects data and its potential to support a change to the existing MCLG.

Section 7 presents an overall conclusion of the results of the health effects review, including identification of contaminants for which OW identified new health effects assessments or information that may support an update to the current MCLG based on health effects information alone.

Section 8 includes the references cited throughout this document. Studies referenced in this assessment are cited as "Author Last Name, Publication Year, HERO ID" and are available in EPA Health and Environmental Research Online (HERO): A Database of Scientific Studies and References. The HERO ID is a unique identifier for publications available in HERO. Additional study metadata are publicly available and can be obtained by searching for the HERO ID on the public-facing webpage available here: https://hero.epa.gov/.

3 Background

EPA completed its first Six-Year Review (referred to here as "Six-Year Review 1;" SYR 1) in July 2003 {U.S. EPA, 2002b, 6324890; U.S. EPA, 2003b, 9093470}. In SYR 1, EPA evaluated the information available at that time on the key elements of the review process for 68 chemical contaminants covered under various NPDWRs. The assessment of health effects for these 68 chemicals was presented in the Six-Year Review: Chemical Contaminants Health Effects Technical Support Document {U.S. EPA, 2003c, 10721503}. Five chemicals (beryllium, 1,1-dichloroethylene, lindane, oxamyl, and picloram) were identified as potentially qualifying for revision on the basis of new EPA health assessments, independent of technological feasibility considerations (i.e., analytical and treatment technology) and occurrence data. The SYR 1 health assessment also identified three chemical contaminants (cyanide, di(2-ethylhexyl)adipate, and thallium) as high priority for reevaluation due to reproductive and/or developmental information resulting from the literature search and new assessments available at that time. Fluoride was also identified as a candidate for reevaluation due to information on dental, bone, and cancer effects. In completing SYR 1, the agency determined that it was not appropriate to revise any of the sixty-eight chemical NPDWRs considered at that time {U.S. EPA, 2003d, 9193470}.

The agency completed the health effects review for the second Six-Year Review in October 2009 {U.S. EPA, 2010a, 10493651; U.S. EPA, 2009a, 1261609} (referred to here as "Six-Year Review 2;" SYR 2). Under SYR 2, the health assessments of 71 chemicals were reviewed. Lead and copper were not included under SYR 2 because of ongoing efforts initiated in 2006 to revise the Lead and Copper Rule. However, five chemicals (arsenic, uranium, combined radium (226 and 228), alpha particle emitters, and beta particle and photon emitters) not considered during SYR 1, for which new regulations had been promulgated, were considered during SYR 2.

During SYR 2, new EPA health assessments were identified that could impact maximum contaminant level goals (MCLGs) for 14 contaminants (alachlor, barium, 2,4-D (2,4-dichlorophenoxyacetic acid), 1,1-dichloroethylene, diquat, endothall, glyphosate, hexachlorocyclopentadiene, lindane, oxamyl (vydate), picloram, toluene, 1,1,1-trichloroethane, and xylenes (total)). EPA also identified five contaminants (chromium, nitrate, nitrite, selenium, and 1,2,4-trichlorobenzene) for which new literature was available to support the potential need for new health effects assessments and two contaminants (atrazine and simazine) that warranted further evaluation based on availability of new health effects data {U.S. EPA, 2009a, 1261609}.

Considering analytical methods, technology, and other factors along with health assessments during SYR 2, EPA identified four NPDWR chemical contaminants (acrylamide, epichlorohydrin, tetrachloroethylene, and trichloroethylene) as candidates for revision.

The agency completed the health effects review for the third Six-Year Review (referred to here as "Six-Year Review 3;" SYR 3) in December 2016 {U.S. EPA, 2010a, 10493651; U.S. EPA, 2016c, 6557097}. Under SYR 3, EPA evaluated the information available at that time for 73 contaminants. Twelve of these NPDWRs were being considered as part of ongoing or pending regulatory actions and 19 were determined to have an EPA health effects assessment in process or planned by an EPA program office. EPA conducted a health effects review including a health assessment search (web-based) for each of the remaining 42 chemicals to inform potential MCLG derivation. For all of the 42 chemicals, a literature search of scientific literature databases was conducted to consider the new literature in light of EPA health assessment nominations. During SYR 3, new EPA health assessments were identified that could impact MCLGs for 22 contaminants (alachlor, barium, beryllium, carbofuran, cyanide, 1,1-dichloroethylene, cis-1,2- dichloroethylene, 2,4-D (2,4-dichlorophenoxyacetic acid), diquat, endothall, fluoride, hexachlorocyclopentadiene, lindane, methoxychlor, oxamyl (vydate), picloram, selenium,

styrene, toluene, 1,1,1-trichloroethane, 1,2,4- trichlorobenzene, and xylenes (total)). Considering analytical methods, technology, and other factors along with health assessments during SYR 3, EPA identified no NPDWR chemical contaminants as candidates for revision; however, EPA nominated several microbial contaminants and disinfection byproducts as candidates for revision {U.S. EPA, 2017a, 5638481}.

Detailed information on all chemicals included in SYR 3 can be found in the Six-Year Review 3—Health Effects Assessment for Existing Chemical and Radionuclide NPDWRs —Summary Report {U.S. EPA, 2016c, 6557097}.

3.1 How EPA Sets the MCLG

Because the identification of contaminants as candidates for possible NPDWR revision based on health effects is dependent on whether the MCLG could change, a brief explanation of MCLG derivation is helpful. The MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse health effects occur, allowing for an adequate margin of safety. As the name implies, an MCLG is a health goal; it is not an enforceable standard. The maximum contaminant level (MCL) is the maximum permissible level of a contaminant in water that can be delivered to any user of a public water system, and it is an enforceable standard. The MCL is set as close as feasible to the MCLG, taking into consideration cost and technical factors such as the analytical minimal reporting level[2] and treatment technology limitations.

To establish the MCLG, EPA assesses the peer reviewed science examining cancer and noncancer health effects associated with oral exposure to the contaminant. For linear carcinogenic contaminants, where there is a proportional relationship between dose and carcinogenicity at low concentrations, EPA has a long-standing practice of establishing the MCLG at zero (see {U.S. EPA, 1998a, 10442462; U.S. EPA, 2000b, 10442463; U.S. EPA, 2001a, 10442464}. For nonlinear carcinogenic contaminants, contaminants that are suggestive carcinogens, and non-carcinogenic contaminants, EPA typically establishes the MCLG based on an RfD. An RfD is an estimate of a daily exposure to the human population (including sensitive populations) that is likely to be without an appreciable risk of deleterious effects during a lifetime. A nonlinear carcinogen is a chemical agent for which the associated cancer response does not increase in direct proportion to the exposure level and for which there is scientific evidence demonstrating a threshold level of exposure below which there is no appreciable cancer risk.

Establishing the MCLG for a chemical has historically been accomplished in one of three ways depending upon a three-category cancer classification approach (Categories I, II, and III) {U.S. EPA, 1985a, 9207; U.S. EPA, 1991a, 5499}. The categories are based on the available evidence of carcinogenicity after exposure via ingestion. Today, EPA uses a similar approach based on updated EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005a, 6324329}.

- Category I chemicals have "strong evidence [of carcinogenicity] considering weight of evidence, pharmacokinetics, and exposure" {U.S. EPA, 1985a, 9207; U.S. EPA, 1991a, 5499}. EPA's 2005 Cancer descriptors associated with this category are: "carcinogenic to humans" or "likely to be carcinogenic to humans" {U.S. EPA, 2005a, 6324329}. EPA's policy under SDWA is to set MCLGs for these chemicals at zero because it is assumed, in the absence of other data, that there is no known threshold for carcinogenicity {U.S. EPA, 1985a, 9207; U.S. EPA, 1991a, 5499}. In

[2] The minimal reporting level refers to the quantitation level selected by EPA to ensure reliable and consistent results. It is the minimum quantitation level of a contaminant that can be achieved with 95 percent confidence by capable analysts at 75 percent or more of the laboratories using a specified analytical method {U.S. EPA, 2021c, 9640861}.

cases when there is sufficient evidence to determine a nonlinear cancer mode of action (MOA), the MCLG is based on the RfD approach described in Section 3.1.1.

- Category II chemicals have "limited evidence [of carcinogenicity] considering weight of evidence, pharmacokinetics, and exposure" {U.S. EPA, 1985a, 9207; U.S. EPA, 1991a, 5499}. EPA's 2005 Cancer descriptor associated with this category is: "suggestive evidence of carcinogenic potential" {U.S. EPA, 2005a, 6324329}. For these contaminants, the MCLG is based on noncancer effects and therefore the RfD approach is used {U.S. EPA, 1985a, 9207; U.S. EPA, 1991a, 5499}.
- Category III chemicals have "inadequate or no animal evidence [of carcinogenicity]" {U.S. EPA 1985a, 9207; U.S. EPA, 1991a, 5499}. EPA's 2005 cancer descriptors associated with this category are: "inadequate information to assess carcinogenic potential" and "not likely to be carcinogenic to humans" {U.S. EPA, 2005a, 6324329}. For these contaminants, the MCLG is based on noncancer effects and therefore the RfD approach is used.

For additional information on cancer classification and the approaches used to establish an MCLG, refer to Table 3-1.

3.1.1 Non-Carcinogens

For chemicals exhibiting a noncancer threshold for toxic effects (e.g., Category II or III; see {U.S. EPA, 1985a, 9207; U.S. EPA 1991a, 5499}) and for nonlinear carcinogens (e.g., see {U.S. EPA, 2005a, 6324329}), EPA has historically established the MCLG based on a toxicity value (typically an RfD), but similar toxicity values may also be used when they represent the best available science (e.g., ATSDR Minimal Risk Level). In addition to a toxicity value, the calculation of a noncancer MCLG considers exposure factors including body weight and drinking water intake of a target population, and a relative source contribution (RSC). A brief description of how EPA calculates or identifies these factors is included in the following sections.

3.1.1.1 Calculating the RfD

The RfD is 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 non-cancer effects during a lifetime. The RfD is reported in mg/kg/day and is derived as follows:

RfD (mg/kg/day) = BMDL or NOAEL or LOAEL

$$RfD = \frac{BMDL\ or\ NOAEL\ or\ LOAEL}{UF}$$

Where:

BMDL = lower confidence limit on the benchmark dose (mg/kg/day)

NOAEL = no-observed-adverse-effect level (mg/kg/day)

LOAEL = lowest-observed-adverse-effect level (mg/kg/day)

UF = uncertainty factor

Benchmark Dose Lower Confidence Limit (BMDL): Benchmark dose (BMD) modeling can be performed to identify a dose level that causes a defined level of change in the critical effect. Since the BMD modeling and the determination of the BMD and BMDL is dependent on a predetermined change in response rate of an adverse effect compared to background (or the benchmark response (BMR)), it is

critical to select an appropriate BMR in the BMD modeling process. For quantal data, an excess risk of 10% generally has been the default BMR because the 10% response is at or near the limit of sensitivity in most cancer and noncancer bioassays. A lower BMR can be used if a study has greater-than-usual sensitivity or if there is a biological rationale (e.g., developmental effects), although the BMD at a 10% response (BMD_{10}) and the lower 95% confidence limit on the BMD_{10} ($BMDL_{10}$) are usually presented for comparison purposes. For continuous data, if there is a minimal level of change in the endpoint that is generally considered to be biologically significant, then that amount of change can be used to define the BMR {U.S. EPA, 2012a, 1239433}. In the absence of these data on the adverse response level, a change in the mean equal to one standard deviation (1 SD) from the control mean is generally used {U.S. EPA, 2000c, 10721895; U.S. EPA, 2012a, 1239433}.

BMD modeling is the preferred approach for deriving RfDs instead of using a NOAEL or LOAEL. The BMDL is a dose that is determined by fitting a flexible mathematical model to the data. The BMD is the central estimate of that dose, and the BMDL is the corresponding lower limit of a one-sided 95% confidence interval on the BMD.

The Benchmark Dose Technical Guidance {U.S. EPA, 2012a, 1239433} describes a hierarchy by which benchmark responses (BMRs) are selected, with the first and preferred approach being the use of a biological or toxicological basis to define what minimal level of response or change is biologically significant. If that biological or toxicological information is lacking, the guidance document recommends BMRs that could be used in the absence of information about a minimal clinical or biological level of change considered to be adverse—specifically, a BMR of one SD change from the control mean for continuous data or a BMR of 10% extra risk for dichotomous data. When severe or frank effects are modeled, a lower BMR can be adopted. For example, developmental effects are frequently serious effects, and the Benchmark Dose Technical Guidance suggests that studies of developmental effects can support lower BMRs. BMDs for these effects may employ a BMR of 0.5 SD change from the control mean for continuous data or a BMR of 5% for dichotomous data {U.S. EPA, 2012a, 1239433}. A lower BMR can also be used if it can be justified on a biological and/or statistical basis.

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which no biologically significant increases in the frequency or severity of an adverse effect between the exposed population and its appropriate control are observed; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest exposure level at which biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group are observed.

Uncertainty Factor (UF): The BMDL, NOAEL, or LOAEL used for deriving the RfD can be determined from animal or human data. In calculating an RfD, the BMDL, NOAEL, or LOAEL is divided by a composite uncertainty factor (UFc). The composite UF is a product of one or more component UFs, each one accounting for a different source of uncertainty introduced either by variability or the absence of information (see below). Each component UF presented below may range between 1 and 10. The magnitude of the value is determined using a combination of scientific evidence and professional judgment {U.S EPA, 2002d, 88824}.

Some past assessments also used a modifying factor (MF) in the calculation of UFc, but this practice was discontinued {U.S. EPA, 2002b, 6324890}. The MF was intended to account for the scientific uncertainties of the study and database not explicitly covered by the standard UFs (e.g., the completeness of the overall database). The current practice is to address these uncertainties with a database UF. Based

on the EPA guidance for RfD determination, the total UF may not exceed 3,000 {U.S. EPA, 2002d, 88824}.

The following paragraphs describe the component UFs according to methods described in EPA's *Review of the Reference Dose and Reference Concentration Processes* {U.S. EPA, 2002d, 88824}. In addition to the considerations suggested below, others may be appropriate depending upon data availability, applicability, and quality. In particular, additional considerations are used in deriving RfDs for nutritionally essential elements, such as recommended intake.

- UF_H (human to sensitive human): A factor of 10 is used as the default when data from human populations are lacking or deficient, as well as when the data used to derive the RfD are from studies on average healthy humans. A factor of 3 can be used when the sensitivity of the human population used in the study is judged to be between that of sensitive and average healthy humans, such as when some, but not all, significant contributors to sensitivity are addressed, or when the study population is large enough to capture significant population variability. Chemical-specific data can also be used to adjust this factor when adequate data are available. A factor of 1 is used when the data are from a good-quality epidemiology study evaluating effects in a sensitive population.
- UF_A (animal to human): A factor of 10 is used as the default when extrapolating valid results from experimental animal studies, when studies in humans are not available or are inadequate. A factor of 3 can be used when results are obtained from an animal species that is physiologically similar to humans such as nonhuman primates, or when pharmacokinetic modeling is used in extrapolating from the animal data {U.S. EPA, 1994a, 6488}. Chemical-specific data can also be used to adjust this factor when adequate data are available. A factor of 1 can be used when results are from an animal species that is known to be more sensitive than humans to the chemical of interest, or when comparative metabolic and/or toxicity data show that the experimental animal responds to the chemical or agent in a manner that is the same or very similar to the way that a human would respond.
- UF_L (LOAEL to NOAEL): A factor of 10 is used as the default when deriving an RfD from a LOAEL instead of a NOAEL. A factor of less than 10 (typically 3) can be used when there is sufficient evidence to suggest that the LOAEL used is based on an effect of minimal adversity or when the dose-response analysis for the collection of similar studies demonstrates that the difference between an effect and no effect level is less than 10. A factor of 1 is used when the critical effect level is a NOAEL or when BMD modeling (i.e., a BMDL) was used to identify the point of departure. The BMDL has been used as an alternative to the NOAEL as a point of departure in noncancer risk assessment.
- UF_S (subchronic to chronic): A factor of 10 is used as the default when less-than-chronic results from studies of subchronic duration in humans or experimental animals are used in the absence of useful long-term exposure human or animal data. A factor of 3 may be used for intermediate data, such as when some studies on chronic exposures are available but did not evaluate parameters shown to be affected in studies of shorter exposure duration. A factor of 1 is used when the RfD is derived from a chronic study. A factor of 1 also can be used when results from a subchronic exposure study are used, if it is known that the study is more sensitive than any available chronic studies, or that the study evaluated the full duration of relevance for the critical effect (e.g., for certain reproductive or developmental effects or relevant acute effects such as cholinesterase inhibition).
- UF_D (completeness of database): This UF is used when deriving a risk value from an "incomplete" database. The intermediate factor of 3 is often used when there is a single data gap (e.g., missing a multigenerational reproduction study, or missing a systemic toxicity study in one species). The minimum database for a high confidence RfD includes two systemic toxicity studies of chronic or subchronic duration in different species, a two-generation reproductive study, and

two developmental toxicity studies in different species. For systemic toxicity studies, the key consideration when determining an appropriate UF is whether a range of endpoints was evaluated; duration extrapolation, if relevant, is addressed by UF_S. The minimum dataset for a low confidence chronic RfD is a single subchronic study {U.S. EPA, 2002d, 88824}). Note that EPA did not generally use the UF_D prior to approximately 1998 because database deficiencies were addressed with the use of an MF, as discussed above. After 1998, the UF_D was adopted by the IRIS program. The UF_D was not used for regulations by OW until 1997, when some chemicals were assigned database factors. Therefore, some older RfDs that were developed by EPA based on incomplete databases might be 3- to 10-fold lower if current UF guidelines were followed. This is the case for several regulated chemicals that have since been reevaluated by IRIS or OPP resulting in the addition of a UF_D to the composite UF for the same critical effects and point of departure as the one used for the regulation.

3.1.1.2 Calculating the MCLG

A noncancer MCLG is designed to be protective of noncancer effects over a lifetime of exposure with an adequate margin of safety, including for sensitive populations and life stages, consistent with SDWA 1412(b)(3)(C)(i)(V) and 1412(b)(4)(A). For non-carcinogens, the MCLG is derived from the RfD, (discussed in the previous section). Historically, a Drinking Water Equivalent Level (DWEL), a drinking water lifetime exposure level, assuming 100% drinking water exposure at which adverse, non-carcinogenic health effects would not be expected to occur, has also been determined from the RfD. The DWEL is derived as follows:

$$\text{DWEL (mg/L)} = \frac{Oral\ RfV \times BW}{DWI}$$

Where:

Oral RfV = oral reference value (mg/kg/day) identified from the selected human health assessment

BW = body weight (70 kg for adults, 10 kg for children) based on NHANES III database (1988–1994) and a 1989 study conducted by the National Cancer Institute {U.S.EPA, 2000, 19428}

DWI = drinking water intake (2 L/day for adults, 1 L/day for children) based on the U.S. Department of Agriculture's 1994–1996 CSFII analysis ({U.S. EPA, 2000, 19428}

The DWEL value is then multiplied by the relative source contribution (RSC) to calculate an MCLG. The RSC considers other known or potential sources of exposure. Specifically, it represents the percentage of the total exposure attributed to drinking water sources {U.S. EPA, 2000c, 19428}, with the remainder of the exposure allocated to all other routes or sources. The purpose of the RSC is to ensure that the level of a contaminant (e.g., MCLG value), when combined with other identified sources of exposure common to the population of concern, will not result in exposures that exceed the RfD. For more information on RSC, please see Section 4 of EPA's Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health {U.S. EPA, 2000c, 19428}.

3.1.2 Carcinogens

As previously stated, EPA establishes MCLGs of zero for carcinogens classified as "carcinogenic to humans" or "likely to be carcinogenic to humans" (Category I) for which there is insufficient information to determine that a carcinogen has a threshold below which there are no carcinogenic effects {U.S. EPA, 1998a, 10442462; U.S. EPA, 2000b, 10442463; U.S. EPA, 2001a, 10442464}. This section presents EPA's guidance for assessing carcinogens.

3.1.2.1 Classification

For drinking water contaminants regulated prior to the 1996 SDWA Amendments, OW followed the three-category regulatory cancer classification system (Categories I, II, or III) described below. These categories specify decisions as to the degree of concern for an agent's carcinogenic potential as a contaminant of drinking water and define to some extent the approach to risk management that is taken for establishing MCLGs.

EPA also used the six alphanumeric categories (A, B1, B2, C, D, and E) of the 1986 cancer guidelines {U.S. EPA, 1986a, 199530} in establishing MCLGs. The six-group classification system is often equated to the three-category system in the NPDWR Federal Register announcements. Table 3-1 describes the three categories and, with few exceptions (e.g., beryllium), their usual equivalent alphanumeric classification. If a chemical was a known or probable human carcinogen by the oral route (Category I, generally Group A or B), the MCLG was generally set at zero because it is assumed, in the absence of other data, that there is no known threshold for carcinogenicity. If a chemical is in Group C (Category II), the MCLG was derived using the RfD approach (as described in the previous section), and an additional risk management safety factor of 1 to 10 was applied to account for possible carcinogenicity. If a chemical is placed into Group D or E (Category III), the MCLG was derived using the RfD approach described in the previous section. The methodology used under this approach for establishing MCLGs for chemicals with varying degrees of evidence of carcinogenicity is summarized in Table 3-1.

Proposed revisions to the 1986 cancer guidelines were released in 1996 and 1999 {U.S. EPA, 1996a, 83524; U.S. EPA, 1999a, 4440451} as interim guidelines and both revisions were applied to official final EPA assessments. Other interim cancer guidelines were published but not used in official final EPA assessments. These revised versions of the guidelines, like the current guidelines (finalized in 2005) described below, emphasized the use of descriptors coupled with a narrative based on the entire weight of evidence (rather than a cancer classification), and emphasized MOA. However, the 1996 and 1999 versions used somewhat different sets of descriptors and different definitions of the data supporting each descriptor than the 2005 guidelines. Under the proposed 1996 guidelines, there were just three broad categories of descriptors: known/likely, cannot be determined, and not likely. Under the draft 1999 guidelines there were five categories of descriptors: "carcinogenic to humans," "likely to be carcinogenic to humans," "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential," "data are inadequate for an assessment of human carcinogenic potential," and "not likely to be carcinogenic to humans." The 1996 proposed and 1999 draft guidelines were also generally consistent with the 2005 approach to quantitation (see Section 3.1.2.2), although they differed in some minor details with respect to the modeling and the terminology used to identify the point of departure (ED vs. BMD).

Under the 2005 guidelines, a descriptive weight of evidence judgment is made, based on all available animal, human, and mechanistic data, as to the likelihood that an agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Under the 2005 guidelines, descriptive terms for carcinogenicity replaced the terms used in the 1999 draft guidelines, which themselves replaced the 1986 alphanumeric cancer group designations, as described above. A cancer narrative is also included under the 2005 guidelines to provide a more complete description of the weight of evidence and conditions of carcinogenicity. The suggested descriptive terms under the 2005 guidelines are as follows:

- "carcinogenic to humans,"
- "likely to be carcinogenic to humans,"
- "suggestive evidence of carcinogenic potential,"
- "inadequate information to assess carcinogenic potential," and
- "not likely to be carcinogenic to humans."

Compound descriptors are possible if a chemical has different carcinogenic responses with different routes of exposure, dose, or mode of action MOA.[3] MOA information enters into both the qualitative and quantitative portions of the assessment. The MOA determines such issues as the human relevance of the observed tumors and any route-specific differences (e.g., carcinogenic in the respiratory tract via the inhalation route, but not carcinogenic via the oral route). MOA must be considered separately for every target organ. Because of these considerations, one cannot directly translate the cancer classifications and risk values under the 1986 guidelines to narrative statements and risks under the 2005 guidelines. A full consideration of the weight of evidence, including consideration of any available MOA data, would be needed for an assessment under the 2005 guidelines.

The cancer classifications in this health review for SYR 4 chemicals are based only on the agency's most recent available formal risk assessments. Note that EPA cancer assessments conducted between 1996 (following publication of the proposed guidelines) and 2001, when the agency published a Federal Register notice {U.S. EPA, 2001b, 11328258} authorizing use of the 1999 draft guidelines on an interim basis, often presented two sets of cancer classifications—one following the 1986 guidelines, and one following the classification system of the then-most current official version of the pre-2005 guidelines. OPP assessments conducted during that time period only used the 1986 guidelines. Table 3-1 compares the three-category approach, as well as the 1986, 1999, and 2005 cancer guidelines.

Table 3-1. EPA Three-Category Approach and Corresponding 1986, 1999, and 2005 Cancer Guidelines

Three-Category Approach for Establishing Potential MCLGs	Corresponding Five-Group Classification System of 1986 Cancer Guidelines	Corresponding Five-Group Classification System of the 1999 Draft Cancer Guidelines	Corresponding Classification System of 2005 Cancer Guidelines
MCLG generally set at zero			
Category I: Known or probable human carcinogen: Strong evidence of carcinogenicity Sufficient human or animal evidence of carcinogenicity.	**A: Human carcinogen:** Sufficient evidence from epidemiological studies to support a causal association.	**Carcinogenic to humans:** Convincing epidemiologic evidence demonstrating causality between human exposure and cancer.	**H: Carcinogenic to human:** Strong evidence of human carcinogenicity.
	B Probable human carcinogen: **B1:** Limited evidence of carcinogenicity from epidemiological studies. **B2:** Inadequate evidence or no data from epidemiological studies; sufficient evidence from animal studies.	**Likely to be carcinogenic to humans:** Data are adequate to demonstrate carcinogenic potential to humans.	**L: Likely to be carcinogenic to humans:** Weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "carcinogenic to humans."

[3] Mode of action is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. It is contrasted with "mechanism of action," which implies a more detailed understanding and description of events.

Three-Category Approach for Establishing Potential MCLGs	Corresponding Five-Group Classification System of 1986 Cancer Guidelines	Corresponding Five-Group Classification System of the 1999 Draft Cancer Guidelines	Corresponding Classification System of 2005 Cancer Guidelines
MCLG based on the RfD with an additional risk management safety factor of up to 10 to account for possible carcinogenicity[a], or is based on excess cancer risk range of 10^{-5} to 10^{-6}			
Category II: Limited evidence of carcinogenicity: Some limited but insufficient evidence of carcinogenicity from animal data.	**C: Possible human carcinogen:** Limited evidence of carcinogenicity in animals in the absence of human data.	**Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential:** Evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects but is judged not sufficient for a conclusion as to human carcinogenic potential.	**S: Suggestive evidence of carcinogenic potential**: The weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion.
MCLG established using the RfD approach			
Category III: Inadequate or no evidence of carcinogenicity in animals	**D: Not classifiable as to human carcinogenicity:** Inadequate human and animal evidence of carcinogenicity, or no data available.	**Data are inadequate for an assessment of human carcinogenic potential**: Data are judged inadequate to perform an assessment.	**I: Inadequate Information to Assess Carcinogenic Potential:** Available data are judged inadequate for applying one of the other descriptors.
	E: Evidence of non-carcinogenicity for humans: No evidence of carcinogenicity in two different animal species, or in both epidemiological and animal studies.	**Not likely to be carcinogenic to humans:** Data are considered robust for deciding that there is no basis for human hazard concern.	**N: Not likely to be carcinogenic to humans:** Data are considered robust for deciding that there is no basis for human hazard concern.
			Multiple Descriptors[b]: The 2005 guidelines allow for more than one descriptor.

Notes:

[a] If a chemical was previously Group C under the 1996 Cancer Guidelines and updated to Group S under the 2005 Cancer Guidelines in a more recent EPA assessment, a risk management safety factor of 10 will be maintained for consistency, if originally applied.

[b] For example, an agent could be labeled as L/N because it is "likely to be carcinogenic" above a specified dose but "not likely to be carcinogenic" below that dose because a key event in tumor formation does not occur below that dose.

A risk management safety factor of 10 was applied to calculate the existing MCLGs for eight contaminants including atrazine, beryllium, 1,1-dichloroethylene, di(2-ethylhexyl)adipate, styrene, p-dichlorobenzene, 1,1,2 trichloroethane, and simazine. For SYR 4, risk management safety factors were removed for atrazine, beryllium, 1,1-dichloroethylene, simazine, and p-dichlorobenzene based on updated cancer classifications. Detailed information can be found in the chemical specific summaries found in Section 6.

3.1.2.2 Quantification

The quantitative aspect of cancer assessment also changed between the 1986 and 2005 guidelines. Under the 1986 guidelines, the cancer risk was calculated by fitting a model to the tumor data, and then calculating a 95% upper confidence limit on one of the coefficients in the model. The Linear Multistage Model was the one used most frequently; a few chemicals were quantified based on other risk models.

The resulting number was the q1* (also known as the slope factor), producing an upper bound on the risk. In addition, in the 1986 guidelines, human equivalent doses were estimated from animal data using a scaling factor of body weight to the 2/3 power.

Under the 2005 guidelines, a two-step process is used for the quantitation step. First, a model is used to fit a dose-response curve based on the doses and associated tumors from the cancer bioassay. The model is used to identify the point of departure (POD), i.e., the dose that is used for extrapolation to the low-dose region based on the BMD associated with a significant increase in tumor incidence above the control. According to the 2005 guidelines {U.S. EPA, 2005a, 6324329}, the POD is the lowest dose that is adequately supported by the data. The ED_{10} (the dose corresponding to a 10% increase in tumors), and the LED_{10} (the 95% lower confidence limit on that dose) are also reported and are often used as the POD. Some of the more recent assessments use the BMD/BMDL terminology rather than the ED/LED terminology. In the 1996 guidelines and in all later versions, the default for calculating human equivalent dose for oral exposure uses a scaling factor of body weight to the 3/4 power ((body weight)$^{3/4}$) {U.S. EPA, 2011a, 752972}.

In the second step of the low-dose extrapolation, one extrapolates from the POD to the low-dose region of interest for environmental exposures. The approach for extrapolation depends on the MOA for carcinogenesis. If the chemical causes cancer through a mutagenic change to DNA, or if the MOA for causing cancer is not known, this extrapolation is conducted by drawing a line from the POD to the origin (zero dose, zero tumors, corrected for the background response). The slope of the line gives the unit risk (risk per unit dose, or risk per (mg/kg/day)). If there was a positive tumor response at all bioassay doses, the calculated slope is often very similar to that calculated using the q1* approach. In addition, under the supplemental guidance {U.S. EPA, 2005b, 88823}, affirmative determination of a mutagenic MOA (as opposed to defaulting to a mutagenic MOA based on insufficient data or limited data indicating potential mutagenicity) determines if age adjustment dependent factors (ADAFs) are applied in the quantification of risk to account for additional sensitivity of children.

If the chemical is shown to cause cancer via a MOA that is not linear at low doses, and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses, a nonlinear extrapolation is conducted. In earlier versions of the cancer guidelines {U.S. EPA, 1996a, 83524; U.S. EPA, 1999a, 4440451} the point of departure was compared to the exposure of interest, resulting in a margin of exposure (MOE). However, these earlier guidelines did not define the acceptable MOE value. The 2005 guidelines state that "where tumors arise through a nonlinear MOA, an oral reference dose or inhalation reference concentration, or both, should be developed in accordance with EPA's established practice of developing such values, taking into consideration the factors summarized in the characterization of the POD." In these cases, an RfD-like value is calculated based on the key event[4] for carcinogenesis or the tumor response.

[4] The key event is defined as an empirically observed precursor step that is itself a necessary element of the mode of action or is a biologically based marker for such an element.

4 Six-Year Review 4 Methods

This section summarizes the methods used for the identification and selection of key peer-reviewed health assessments, calculation of potential MCLGs, and literature searches for SYR 4 contaminants. For contaminants in which there has been a change in the RfD since rule promulgation, EPA calculated a potential MCLG, which is a candidate value used as a tool to identify regulated chemicals for which new science may support a change to the existing MCLG.

4.1 Health Assessments

4.1.1 Assessment Identification

In order to identify final peer-reviewed qualifying health assessments, EPA conducted a systematic web-based search between September and November 2020 for EPA and other authoritative sources of human health effects assessments for each regulated drinking water chemical contaminant postdating rule finalization. Health effects assessments are considered qualifying if they 1) derived one or more toxicity value (e.g., RfD, CSF) and/or a cancer descriptor based on the best available science; 2) underwent a documented peer-review process; 3) are publicly available and final; and 4) were developed using HHRA methods that are comparable to EPA HHRA principles and approaches (e.g., a weight of evidence approach); 5) are published from an authoritative body that routinely develops health effects assessments (e.g., ATSDR). Recognizing that health assessment methodologies vary across sources, Appendix A describes the differences that were identified for transparency. For currently registered pesticide chemicals, one source of assessments was used:

EPA OPP health assessments (e.g., Reregistration Eligibility Decisions [REDs] or Health Effects Division Human Health Risk Assessments [HED HHRAs])For all other chemicals, sources of qualifying assessments included the following EPA program offices, other national and international programs, and state programs:

- EPA Office of Water (OW) Health Assessments: Drinking Water Standards and Health Advisory documents (DWSHAs), Health Effects Support Documents (HESDs)
- EPA ORD IRIS Assessments
- EPA ORD Provisional Peer-Reviewed Toxicity Values (PPRTVs)
- EPA OPPT TSCA Risk Evaluations
- Center for Disease Control and Prevention's ATSDR Toxicological Profiles
- Health Canada (HC) Guidelines for Drinking Water Quality (GDWQ)
- World Health Organization (WHO) Background Documents for Development of WHO GDWQ
- CalEPA's PHGs
- Other publicly available state and federal assessments that have been externally peer-reviewed

4.1.2 Assessment Selection for List B Contaminants

After identifying all of the available qualifying final peer-reviewed health effects assessments (see Section 4.1.1), EPA followed a structured and transparent process to select the assessment that could be used to derive a potential MCLG. The systematic approach described herein was used to select a drinking water relevant assessment based on the best available science. In cases when multiple new health assessments were identified for a given chemical, EPA reviewed the assessments and applied the following decision logic to select the health assessment for potential MCLG derivation.

For chemicals regulated under EPA's FIFRA, EPA always selected EPA OPP health assessments developed to support FIFRA registration decisions. If the contaminant is an industrial chemical regulated

under the TSCA and the final OPPT risk evaluation is relevant to the drinking water pathway, the most current assessment, and based on the best available science, it was selected.

For all other chemical contaminants, including industrial chemicals without a recent final TSCA risk evaluation and pesticide chemicals with uses no longer registered under FIFRA, EPA followed a systematic process to select a health assessment to derive potential MCLGs among the qualifying assessments identified. When multiple qualifying assessments were identified for a contaminant, EPA evaluated each assessment by considering a number of factors to discern whether the assessment comports with current agency HHRA practices and uses the best available science. First, the date of publication was used to identify the most recently published health assessment for a chemical as some indication of using the best available science. Second, EPA considered whether the health assessments were developed using HHRA methods that are consistent with current EPA practice (e.g., an RfD based on a newer critical effect, use of benchmark dose modeling, application of systematic review methods) {EPA, 2022c, 10367891}. Finally, EPA used professional judgment to evaluate whether the best available science was used in assessments and its relevance to the drinking water pathway. EPA used the following decision logic when selecting a health assessment among all qualifying assessments to derive a potential MCLG.

EPA selected an EPA health assessment if *any* of the following conditions were met:

1) EPA's assessment was the only available source of a toxicity value and/or cancer descriptor.
2) EPA's assessment was the most current source of a toxicity value and/or cancer descriptor.
3) The toxicity value from a more current toxicological assessment from a source other than EPA was based on the same critical study and was numerically the same as an older EPA toxicity value (i.e., both assessments used the best available science).
4) A more current toxicological assessment from a source other than EPA was available, but it did *not* derive a toxicity value relevant to the drinking water pathway (subchronic or chronic-duration oral RfD or CSF).
5) A more current toxicological assessment from a source other than EPA was available, but it did *not* introduce newer, better science (e.g., the toxicity value was not based on a newer critical study) or use a modeling approach based on the best available science compared to an older EPA toxicological assessment.

EPA selected the toxicity value and/or cancer descriptor from a qualifying available source (see Section 4.1.1) other than EPA if *any* of the following conditions were met:

1) A toxicological assessment from a source other than EPA was the only available one.
2) A more recent toxicological assessment from a source other than EPA introduced the best available science (e.g., the toxicity value was based on a newer, better critical study; updated cancer descriptor) or used a more current modeling approach compared to an older EPA toxicological assessment.

In addition to the above criteria, EPA applied expert judgement when evaluating a set of assessments for a given contaminant because there can be unique challenges. In summary, EPA selects the health effects assessment for a chemical for deriving the potential MCLG based on expert evaluation of a number of criteria, described above, that are designed to identify the drinking water relevant assessment developed using comparable approaches to EPA HHRA methods and based on the best available science.

4.1.2.1 Assessment Selection for Actively Registered Pesticides

FIFRA requires all pesticides sold or distributed in the United States (including imported pesticides) to be registered by EPA. Risk assessment is integral to the process of making decisions about pesticides, both new and existing:

- New pesticides must be evaluated before they can enter the market.
- Existing pesticides must be reevaluated periodically to ensure that they continue to meet the appropriate safety standard.

For currently registered pesticide chemicals, OPP Health Effects Division Human Health Risk Assessments (HHRAs) were selected for potential MCLG derivation in SYR 4. These OPP HHRAs are a component of U.S. EPA Office of Pesticide Programs (OPP) risk assessments, which are used to make safety determinations for pesticides. Pesticide registrations, reregistration decisions, and registration review decisions are based on final OPP risk assessments, which evaluate the most current and best available scientific data and assess the current risks. HED HHRAs undergo peer review by scientific experts prior to publication in the Federal Register. HED HHRAs can be updated at any time based on the availability of new scientific information. For SYR 4, OW coordinated with OPP to ensure the most recent HED HHRA that is the basis of the current pesticide registration decision was selected.

For the SYR 4 key health assessment selection process, the most recent EPA OPP HHRAs and the corresponding toxicity values derived were selected for all pesticides with NPDWRs under SDWA and active registrations and tolerances under FIFRA and FFDCA. OPP applies Food Quality Protection Act (FQPA) Safety Factors to the RfDs to derive Population-Adjusted Doses (PADs). FQPA Safety Factors provide a margin of safety to protect infants and children, taking into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases {EPA, 2002e, 7330218}. In most cases, the PAD and the RfD are the same. When the FQPA Safety Factor is attributed to residual uncertainty with regard to exposure or prenatal and/or postnatal toxicity, the PAD is more protective than the RfD. For this reason, potential MCLGs were calculated using the PADs.

4.2 Application of Updated Exposure Factors to Calculate Potential MCLGs in SYR 4

Exposure factors (EFs) are defined in EPA's Exposure Factor Handbook (EFH) as factors related to human activity patterns, behavior, and characteristics that help determine an individual's exposure to a contaminant {U.S. EPA, 2019, 7267482}. EFs are based on information from publicly available, peer-reviewed studies {U.S. EPA, 2019, 7267482}. The use of EFs in potential MCLG calculations is intended to protect sensitive populations and life stages within the general population from adverse effects resulting from exposure to a contaminant {U.S. EPA, 2000c, 19428}. When deriving a potential MCLG, one of the input values is the body weight-adjusted drinking water intake (DWI-BW) exposure factor. As previously described, the existing MCLGs were derived using an adult BW of 70 kg and DWI of 2 L/day (see Section 3.1.1.2). The adult body weight value of 70 kg is the mean BW of adults from two studies, the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) {WESTAT 2000, 1065491; McDowell, 2000, 11346391} and a 1989 study conducted by the National Cancer Institute {Ershow and Cantor, 1989, 710071}. Similarly, the DWI rate of 2 L/day was used to derive the NPDWRs {U.S. EPA, 1976, 1266059} based on the available data. The 2 L/day drinking water intake value was provided by the consumers-only community water ingestion rate for adults surveyed in the U.S. Department of Agriculture's 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII) analysis {USDA, 1998, 2854331}.

For SYR 4, potential MCLGs were derived using updated drinking water intake and body weight parameters based on more recent data captured in EPA's 2019 Final Chapter 3 update to the EFH {U.S. EPA, 2011b, 10721945; U.S. EPA, 2019, 7267482} (Table 4-1). The updated values in the 2019 EFH for the 90th percentile adult consumers-only tap water intake is 2.5 L/day and the mean adult BW is 80 kg. In addition to adults, other potential target or sensitive populations were considered. In order to identify potential sensitive population(s) or life stage(s) in SYR 4, EPA used two different approaches—an

approach specifically for actively registered pesticides and a different approach for all other chemicals as described below.

Table 4-1. Drinking Water Intake Rate Exposure Factors for a Subset of Life Stages/Populations from the 2019 Exposure Factors Handbook[a]

Population Group	Exposure Parameter (90th percentile)	Data Source (Reference)
General population	33.8 mL/kg/day	Two-day average[b] consumer-only[c] estimates of combined direct and indirect[d] water ingestion of community water for all ages (Table 3-21 {U.S. EPA, 2019, 7267482})
Infants	143 mL/kg/day	Two-day average[b] consumer-only[c] estimates of combined direct and indirect[d] water ingestion of community water from birth to < 1 year (Table 3-21 {U.S. EPA, 2019, 7267482})
Lactating women	46.9 mL/kg/day[e]	Two-day average[b] consumer-only drinking water intake of community water for lactating women (13 to < 50 years) (Table 3-63 {U.S. EPA, 2019, 7267482})
Pregnant women	33.3 mL/kg/day	Two-day average[b] consumer-only drinking water intake of community water for pregnant women (13 to < 50 years) (Table 3-63 {U.S. EPA, 2019, 7267482})
Women of childbearing age	35.4 mL/kg/day	Two-day average[b] consumer-only drinking water intake of community water for women of childbearing age (13 to < 50 years) (Table 3-63 {U.S. EPA, 2019, 7267482})

Notes: mL/kg/day = milliliters per kilogram per day.
[a] Chapter 3, Exposure Factors Handbook {U.S. EPA, 2019, 7267482}
[b] Based on the average of 2 days of consumption reported for each NHANES respondent. If the respondent reported zero consumption on 1 of the 2 days and nonzero consumption on the other day, his/her average consumption would be the average of zero and nonzero consumption. Single day rates can be generated using http://fcid.foodrisk.org/.
[c] Excludes individuals who did not ingest water from the source during the survey period.
[d] Direct water is defined as water ingested directly as a beverage; indirect water is defined as water added in the preparation of food or beverages.
[e] Estimates are less statistically reliable based on guidance published in the Joint Policy on Variance Estimation and Statistical Reporting Standards on NHANES III and CSFII Reports: HNIS/NCHS Analytical Working Group Recommendations {NCHS, 1993, 1005567; U.S. EPA, 2019, 7267482}

4.2.1 Actively Registered Pesticides

For SYR 4 chemicals that are actively registered pesticides, EPA relied on the target population information provided in the OPP risk assessment to identify the sensitive subpopulation for exposure factor selection. For OPP active pesticide risk assessments that identified a target population (i.e., specific age range) not reported in the EFH, EPA used the Joint Institute for Food Safety and Applied Nutrition's Food Commodity Intake Database (FCID) Consumption Calculator Tool[5] which calculates DWI-BWs for specific populations (e.g., sex), life stages, or age ranges from beyond the 2019 EFH data.

4.2.2 All Other Chemicals that Are not Actively Registered Pesticides

For all other SYR 4 chemicals (i.e., those that are not actively registered pesticides), EPA used the information about the critical study that forms the basis for the reference value to inform the identification of potentially sensitive populations or life stages. Although data gaps for a given chemical can make it difficult to identify the most sensitive population, the critical study and critical effect can provide some information about sensitive populations because the critical effect is typically observed at the lowest

[5] Joint Institute for Food Safety and Applied Nutrition's FCID Commodity Consumption Calculator is available at https://fcid.foodrisk.org/percentiles.

tested dose among the available sufficient quality studies. In addition, evaluation of the exposure interval used in the critical study may identify a particularly sensitive population or life stage (e.g., pregnant women, infants, lactating women; see Table 4-1). If a potentially sensitive population or life stage was identified, then an EF for this identified target population can be used to derive the potential MCLG.

The SYR 4 process was based on this generalized approach, described above, and followed a simplified decision logic of three options to identify the potentially sensitive populations or life stages and subsequently select a population for EF application:

1) For chemicals with selected health assessments based on critical effect(s) that were assessed during adulthood (i.e., ≥ 21 years of age in humans per EPA Children's Health Policy (https://www.epa.gov/system/files/documents/2021-10/2021-policy-on-childrens-health.pdf)), the 2019 EF for the 90th percentile, all ages, general population was selected for deriving the potential MCLG (see Table 4-1).
2) For chemicals with selected health assessments based on critical studies (i.e., sometimes multiple studies were selected) that assessed at least one developmental critical effect, the interval of exposure in the critical study was considered. Specifically, when a critical study is based on a critical effect that was observed during development (i.e., the period from gestation to the end of postnatal development) after exposure during gestation *only*, pregnant women and women of childbearing age who might be pregnant were identified as potentially sensitive life stages. In these cases, the EF for women of childbearing age was selected because it has a higher DWI-BW intake rate than for pregnant women and therefore, is protective of the pregnant women's intake rate.
3) In cases when the critical study or studies are based on at least one critical effect that were observed during postnatal development (i.e., during childhood) and exposure was *only* during postnatal development (i.e., not including gestational or adult exposure), the period of postnatal development was identified as a potentially sensitive life stage. In these cases, the EF for infants birth to < 1 year, which has the highest postnatal DWI-BW intake rate, was selected except in cases when a specific age range of sensitivity within postnatal development was indicated by the chemical-specific information.

Based on the availability of updated exposure factors, EPA calculated potential MCLGs for contaminants with a change in the RfD since rule promulgation as follows:

$$\textbf{\textit{Potential MCLG}} = \left(\frac{Oral\ RfD}{DWI - BW}\right) \times RSC \times 1000$$

Where:

Oral RfD = oral reference dose (mg/kg/day)

DWI-BW = body weight-adjusted drinking water intake (mL/kg/day)

RSC = relative source contribution (%)

Conversion factor = 1000× to convert mL (from DWI-BW) to L because the potential MCLG is expressed in mg/L.

4.3 Literature Searches

4.3.1 Literature Searches for List B Chemicals

With the exception of active pesticides (see Table 2-2), a comprehensive search of the peer-reviewed literature was conducted in PubMed® (National Library of Medicine) and Web of Science™ (WoS) for List B chemicals regulated under SDWA. Duplicate references between the two databases were removed with "DeDuper," a software tool developed by ICF {Magnuson, 2018, 7415521}.

4.3.1.1 Search Strings

The search strings consisted of two sets: 1) synonym list and 2) topic filters. For the first set of the search string, synonyms for each chemical were curated by utilizing two databases: EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) and ChemID*Plus* (https://chem.nlm.nih.gov/chemidplus/).

Chemicals are uniquely identified with a DSSTox substance identifier (DTXSID) in the CompTox Chemicals Dashboard. Using the DTXSID, the CompTox Chemicals Dashboard was searched to identify synonyms classified as "valid" or "good" for use in the search string. "Valid" synonyms are those algorithmically generated by systematic naming software or manually curated by DSSTox curation team; "good" synonyms are those identified across a series of public databases {Williams et al., 2017, 4674641}.

The active Chemical Abstract Service Registry Number (CASRN) were retrieved from the CompTox Chemicals Dashboard, and then used to search the ChemID*Plus* database. All synonyms from the database were considered for the search string. Ambiguous and duplicate synonyms were removed prior to execution of the literature search. Ambiguous synonyms were those that lacked sufficient specificity for the chemical of interest. For example, the synonyms "F 30" and "R 30" were removed from the search string for dichloromethane. Synonyms were only added in addition to those retrieved from CompTox Chemicals Dashboard and ChemID*Plus* when there was subject matter expertise. For example, "meta xylene," "ortho xylene," and "para xylene" were included among the synonyms for xylene. The complete list of synonyms used for the chemicals is provided in Appendix C.

The second set of the search string targeted studies with health effects data in humans and animals. In PubMed®, the pre-curated toxicology filter was used, and in WoS, a toxicology filter was curated by using only relevant research areas (listed in Appendix C). Filters for English references were also included in the searches for both databases. Additional terms were only added to the toxicology filters for PubMed® and WoS if there was subject matter expertise. For example, there was specific interest in capturing hematologic diseases for nitrate and nitrite, so "hematologic diseases," "methemoglobinemia," and "blue baby syndrome" were added to the search string.

4.3.1.2 Assignment of Date Limits

The start date of the literature search for each of the chemicals was defined as one year prior to the end date for the literature search from the last Six-Year Review that the chemical was evaluated or the most recently available health assessment, depending on which was most recent. For example, the most recently available health assessment for acrylamide was EPA's Six-Year Review 3—Health Effects Assessment for Existing Chemical and Radionuclide National Primary Drinking Water Regulations—Summary Report {U.S. EPA, 2016c, 6557097}. The literature search cutoff date for this health assessment was December 2015. Therefore, the literature search date limit for acrylamide was designated as December 1, 2014.

In the case that the literature search start and cutoff date were not provided, the start date of the literature search was defined as one year prior to the publication date of the assessment (see Appendix C).

4.3.1.3 Evidence Stream Filtering

SWIFT-Review was utilized to identify the most relevant studies based on evidence stream. SWIFT-Review, developed by Sciome, includes statistical text mining and machine learning methods that were applied to categorize studies by human and animal evidence streams in an effort to prioritize literature search results that were most likely to be relevant to human health. Specifically, the following evidence stream tags were included: Animal (Human Health Models), Environmental Fate, Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Based on the title and abstract, the Animal (Human Health Models) tag included all terms related to animal experimentation or animal models. The primary terms are the specific names of acceptable animals for human health models (e.g., hamsters, mice, pigs, rats, rodents, primates). The Environmental Fate tag included terms related to bioaccumulation, degradation, magnification, transformation, and related chemical processes. The Human (All) tag included terms related to human studies including study types (e.g., case control, cohort, cross-sectional) and study populations (e.g., men, women, disadvantaged, occupational). The Human (Epidemiologic Quantitative Analyses) tag included all terms included within the Human tag with the addition of search strings to capture meta-analyses, systematic reviews, and measures of association (e.g., hazard ratio, odds ratio, prevalence ratio). The In Vitro tag included terms related to cell assays, cell cultures, and cell lines. Specific terms include 3T3, A549, BEAS-2B, CACO-2, CHO cells, HELA, HepG2, HepaRG, Jurkat, and MCF-7. Studies that could not be categorized under one of the defined evidence stream categories outlined above (i.e., Animal (Human Health Models), Environmental Fate, Human (Epidemiologic Quantitative Analyses), In Vitro) were included under a non-specific, albeit potentially relevant to human health, evidence stream No Tag category.

Studies categorized into SWIFT-Review evidence streams not used for this project (i.e., Animal (All), Ecotoxicity (Animal and Plant), Plant, and Physical Chemistry) were excluded from further consideration as they were unlikely to be relevant to human health.

Additional details on the statistical text mining used for identifying the evidence stream tags can be found in Howard et al. (2016, 4149688).

4.3.1.4 Literature Searches for Active Pesticides

Literature searches were not conducted for the pesticide chemicals with NPDWRs under SDWA and active registrations and/or tolerances under the FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA) because EPA periodically reevaluates them to ensure that they continue to meet the appropriate safety standard. The relevant active pesticides for SYR 4 are indicated in Table 2-2.

5 Results for List B Contaminants

EPA evaluated the 62 contaminants under the scope of SYR 4 to determine if there are more recent RfDs and/or cancer risk assessments that might support a change to the MCLG. The chemical summaries presented in Section 6 detail existing and new assessment information, potential MCLGs including derivation parameters, and results of the literature search.

5.1 Findings for Consideration of a Change to the MCLG

Of the 62 List B chemicals evaluated, EPA found new health effects information since the last review cycle (SYR 3) or health effects information that was considered in previous rounds of SYR supporting potential changes to the MCLGs for 29 chemicals. Table 5-1 provides a list of the 29 chemicals along with the original MCLG, potential MCLG, and the health assessment(s) that is the basis for the derivation of the potential MCLG. For 14 of the 29 chemicals, EPA identified health information supporting the potential to raise the MCLG. For the remaining 15 List B chemicals, the agency concluded that based on the analysis of the current information, there is potential for the MCLG to decrease. Although data on health effects suggests a potential to improve public health protection through a revision to the MCLG, factors such as contaminant occurrence and exposure at public drinking water systems, analytical methods, and treatment feasibility are also considered when evaluating whether there is a meaningful opportunity to improve public health through revisions to the current rule.

Table 5-1. Findings for Consideration of a Change to the MCLG

Chemical	Existing MCLG (mg/L)	New Health Assessment of Non-Cancer Effects[a]/Possible Impact on Non-cancer MCLG	New Health Assessment of Cancer Effects [a,b] / Possible Impact to Cancer MCLG	Potential MCLG (mg/L)[c]	Assessment Selected as Basis for Six-Year Review 4 Potential MCLG[d]
Potential to Raise the MCLG					
1,1,1-Trichloroethane	0.2	Yes/Yes	No/No	10	EPA IRIS (U.S. EPA, 2007a, 3004991)
1,1-Dichloroethylene	0.007	Yes/Yes	No/No	0.3	EPA IRIS (2002f, 1739804)
2,4 Dichlorophenoxy-acetic Acid (2,4-D)	0.07	Yes/Yes	No/No	1	EPA OPP (2017b, 10532862)
Alachlor	0	Yes/Yes	No/Yes	0.03	EPA OPP (2007b, 10492629)
Atrazine	0.003	Yes/Yes	Yes/No	0.4	EPA OPP (2018a, 10533087)
Barium	2	Yes/Yes	No/No	5.6	EPA IRIS, (2005c, 11311280)
Beryllium	0.004	Yes/Yes	No/No	0.01	EPA IRIS (1998b, 999207)
Diquat	0.02	Yes/Yes	No/No	0.03	EPA OPP (2020a, 10533339)
Glyphosate	0.7	Yes/Yes	No/No	6	EPA OPP (2017c, 10532909)
Lindane	0.0002	Yes/Yes	Yes/No	0.009	EPA OPP (2004a, 10492448)

Chemical	Existing MCLG (mg/L)	New Health Assessment of Non-Cancer Effects[a]/Possible Impact on Non-cancer MCLG	New Health Assessment of Cancer Effects [a,b] / Possible Impact to Cancer MCLG	Potential MCLG (mg/L)[c]	Assessment Selected as Basis for Six-Year Review 4 Potential MCLG[d]
o-Dichlorobenzene (1,2-Dichlorobenzene)	0.6	Yes/Yes	No/No	2	ATSDR (2006a, 5160103)
p-Dichlorobenzene (1,4-Dichlorobenzene)	0.075	Yes/Yes	Yes/No	0.4	ATSDR (2006a, 5160103)
Picloram	0.5	Yes/Yes	No/No	1	EPA OPP (2020b, 10533340)
Simazine	0.004	Yes/Yes	No/No	0.4	EPA OPP (2018b, 10533123)
Potential to Lower the MCLG					
1,2,4-Trichlorobenzene	0.07	Yes/No	Yes/Yes	0	EPA PPRTV (2009b, 10255709)
Antimony	0.006	Yes/Yes	No/No	0.002	CalEPA (2016a, 10489864)
Carbofuran	0.04	Yes/Yes	No/No	0.0003	EPA OPP (2008a, 10494332)
Cadmium	0.005	Yes/Yes	Yes/No	0.0007	ATSDR (2012a, 2509015)
cis-1,2-Dichloroethylene	0.07	Yes/Yes	No/No	0.01	EPA IRIS (2010b, 10493648)
Cyanide	0.2	Yes/Yes	No/No	0.004	EPA IRIS (2010c, 723657)
Endothall	0.1	Yes/Yes	No/No	0.04	EPA OPP (2015a, 10494329)
Fluoride	4.0	Yes/Yes	No/No	0.9	EPA OW (2010d, 10493692)
Hexachlorocyclopentadiene	0.05	Yes/Yes	No/No	0.04	EPA IRIS (2001c, 10509468)
Methoxychlor	0.04	Yes/Yes	No/No	0.0001	OEHHA (2010, 10489852)
Oxamyl	0.2	Yes/Yes	No/No	0.009	EPA OPP (2017d, 10532947)
Selenium	0.05	Yes/Yes	No/No	0.03	ATSDR (2003a, 2990677)
Styrene	0.1	Yes/Yes	Yes/Yes	0	CalEPA (2010a, 10489854)
Toluene	1	Yes/Yes	No/No	0.06	HC (2014a, 3049488)
Xylenes (total)	10	Yes/Yes	No/No	0.08	HC (2014a, 3049488)

Notes:

[a] This column addresses whether there are new data from an updated EPA or non-EPA assessment since rule promulgation of the NPDWR.

[b] Because the MCLG for a carcinogen with a linear MOA is zero, new data for cancer is only considered for chemicals that are not currently regulated as carcinogens, or for carcinogens that have new data and are now considered to have a threshold for carcinogenicity.

[c] The potential new MCLG numeric values (in mg/L) are based strictly on the health evaluation (not occurrence data or other risk management considerations) using the RSC values currently applied to each NPDWRs except where specifically noted.

[d] In some cases, a newer assessment was available, but the newer assessment did not introduce new science (e.g., no new critical study), did not evaluate the effect of interest (e.g., the assessment only evaluated the non-carcinogenic effects of a known

carcinogen), established a less conservative value and/or was not based on the oral route, therefore, EPA deferred to a previously published EPA assessment.

5.2 Findings for No Consideration of a Change to the MCLG

No potential change to the MCLG was indicated for the remaining 33 List B chemicals listed in Table 5-2 below. For these 33 chemicals, there was either no new health assessment supporting an update to the MCLG, or the updated health assessment did not impact the existing MCLG.

Table 5-2. Findings for No Consideration of a Change to the MCLG

Chemical	Existing MCLG (mg/L)	New Health Assessment of Non-Cancer Effects[a]/ Possible Impact on Non-cancer MCLG	New Health Assessment of Cancer Effects[a]/ Possible Impact to Cancer MCLG	Assessment Selected as Basis for Six-Year Review 4 Potential MCLG[b]
1,2-Dibromo-3-chloropropane (DBCP)	0	Yes/No	Yes/No	EPA PPRTV (2006a, 1258143)
1,2-Dichloroethane	0	Yes/No	Yes/No	EPA IRIS (1987a, 5113321)
1,2-Dichloropropane	0	Yes/No	Yes/No	EPA PPRTV (2016d, 6571209)
1,1,2-Trichloroethane[c]	0.003	No/No	No/No	EPA OW (1992a, 1664368)
Acrylamide	0	Yes/No	Yes/No	EPA IRIS (2010e, 5427469)
Asbestos (fiber > 10 micrometers)	7 million fibers per liter (MFL)	Yes/No	Yes/No	EPA OW (1988a, 10714957)
Benzene	0	Yes/No	Yes/No	EPA IRIS (2003e, 5176611)
Benzo(a)pyrene	0	Yes/No	Yes/No	EPA IRIS (2017e, 3839268)
Carbon tetrachloride	0	Yes/No	Yes/No	EPA IRIS (2010f, 3490869)
Chlordane	0	Yes/No	Yes/No	EPA IRIS (1998, 2509044)
Chlorobenzene	0.1	Yes/No	No/No	EPA IRIS (1989a, 6574259)
Dalapon	0.2	No/No	No/No	EPA OW (1992e, 10492395)
Di(2-ethylhexyl)adipate[c]	0.04	Yes/No	No/No	EPA IRIS (1992b, 6574222)
Di(2-ethylhexyl) phthalate	0	Yes/No	Yes/No	EPA IRIS (1988b, 5113322)
Dichloromethane	0	Yes/No	Yes/No	EPA IRIS (2011c, 808655)
Dinoseb[c]	0.007	No/No	No/No	EPA OW (1992c, 1003105)
Dioxin (2,3,7,8-TCDD)	0	Yes/No	Yes/No	EPA OW (1988c, 2192594) CalEPA (2010b, 10489855)
Endrin	0.002	Yes/No	No/No	EPA IRIS (1992f, 10492397)

Chemical	Existing MCLG (mg/L)	New Health Assessment of Non-Cancer Effects[a]/ Possible Impact on Non-cancer MCLG	New Health Assessment of Cancer Effects[a]/ Possible Impact to Cancer MCLG	Assessment Selected as Basis for Six-Year Review 4 Potential MCLG[b]
Epichlorohydrin	0	Yes/No	No/No	EPA IRIS (1988d, 10532430)
Ethylene dibromide	0	Yes/No	Yes/No	EPA IRIS (2004b, 594429)
Heptachlor	0	Yes/No	Yes/No	EPA IRIS (1987b, 10565929)
Heptachlor epoxide	0	No/No	Yes/No	EPA IRIS (1987c, 10317064)
Hexachlorobenzene	0	Yes/No	Yes/No	EPA OPP (2008b, 1593840)
Nitrate (as N)	10	Yes/No	No/No	EPA IRIS (1991b, 10293342)
Nitrite (as N)	1	Yes/No	No/No	EPA OW (1990a, 10492389)
Pentachlorophenol	0	Yes/No	Yes/No	EPA IRIS (2010g, 6547087)
Silvex (2,4,5-TP)	0.05	Yes/No	No/No	EPA IRIS (1988e, 10270857)
Tetrachloroethylene (PCE)	0	Yes/No	Yes/No	EPA IRIS (2012b, 2826528)
Thallium[c]	0.0005	Yes/No	No/No	EPA OW (1992d, 3994641)
Toxaphene	0	Yes/No	Yes/No	EPA IRIS (1988f, 3123284)
trans-1,2-Dichloroethylene	0.1	Yes/No	No/No	EPA IRIS (2010h, 5185076)
Trichloroethylene (TCE)	0	Yes/No	Yes/No	EPA IRIS (2011d, 3532116)
Vinyl chloride	0	Yes/No	Yes/No	HC GDWQ (2013a, 10528814); EPA IRIS (2000d, 194536)

Notes:

[a] This column addresses whether there are new data from an updated EPA or non-EPA assessment since rule promulgation of the NPDWR.

[b] In some cases, a newer assessment was available, but the newer assessment did not introduce new science (e.g., no new critical study), did not evaluate the effect of interest (e.g., the assessment only evaluated the non-carcinogenic effects of a known carcinogen), established a less conservative value and/or was not based on the oral route, therefore, EPA deferred to a previously published EPA assessment.

[c] There is no health effects information available to impact the MCLG; however, there is a potential to lower the existing MCLG based on the updated exposure factor.

6 Health Effects and Chemical Summaries

The objective of the chemical summaries presented in this section is to provide the basis of the current MCLG, results of the health assessment search, results of the literature search, and potential MCLG derivation parameters for each specific chemical. Each summary concludes with an assessment of the available data and its potential to impact the MCLG, based on health effects. As previously stated, final decisions to revise a NPDWR, including the MCLG, take into account information beyond consideration of toxicity (e.g., occurrence and exposure, treatment technologies, analytical methods).

6.1 Non-TSCA Chemicals

6.1.1 Acrylamide (CAS# 79-06-1 | DTXSID5020027)

6.1.1.1 Basis of the Existing MCLG

EPA published the current NPDWR for acrylamide on January 30, 1991 {U.S. EPA, 1991, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen," according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR imposes a treatment technique requirement that limits the allowable monomer levels in products used during drinking water treatment, storage, and distribution to 0.05 percent acrylamide in polyacrylamide coagulant aids, and limits the dosage of such products to a maximum of 1 mg/L (ppm). Each water system is required to certify, in writing, to the state (using third-party or manufacturer's certification) that the product used meets these residual monomer and use-level specifications {U.S. EPA, 1991a, 5499}.

6.1.1.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for acrylamide that were published prior to the cutoff date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-1.

Table 6-1. Assessments Identified for Acrylamide

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987d, 10510382}	0.0002	NOAEL	Burek et al. (1980, 61311)	–[d]	–	–
EPA OW Health Advisory {U.S. EPA, 1987e, 5926059}	0.0002	NOAEL	Burek et al. (1980, 61311)	–[d]	–	B2[e]
EPA IRIS Toxicological Review {U.S. EPA, 2010e, 5427469}	0.002[f]	HED_{BMDL}	Johnson et al. (1986, 61340)	**0.5**	**Johnson et al. (1986, 61340)**	**L[g]**

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2011a, 10509457}	–[h]	–	–	–[h]	–	–
ATSDR Toxicological Profile {ATSDR, 2012b, 5926041}	0.001[i]	HED_{BMDL}	Friedman et al. (1995, 224307)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; HED_{BMDL} = human equivalent dose to the benchmark dose lower confidence limit.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment did not derive its own CSF but relied on a cancer potency factor of 3.7 $(mg/kg/day)^{-1}$ derived by EPA's Carcinogen Assessment Group {U.S. EPA, 1985b, 10634786}, which was based on data from Johnson et al. (1986, 61340).

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The RfD is based on the human equivalent dose of 0.053 mg/kg/day, which is based on the benchmark dose for a 5% response ($BMDL_5$) of 0.27 mg/kg/day in rats.

[g] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[h] This health assessment did not derive a TDI or CSF for acrylamide, but instead reports margins of exposure based on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.31 mg/kg/day for the induction of mammary tumors in rats and the $BMDL_{10}$ of 0.18 mg/kg/day for the induction of Harderian gland tumors in mice (derived by the Joint Expert Committee on Food Additives {WHO, 2011a, 1021864; WHO, 2011b, 2316673}).

[i] The MRL is based on the lowest predicted human equivalent dose (0.042 mg/kg/day), which was based on a physiologically based pharmacokinetic (PBPK) model-predicted blood time-weighted average (TWA) acrylamide dose for rats ($BMDL_5$ of 0.000240096 mM) (PBPK model of Sweeney et al. (2010, 4662846)).

The health assessment selected for SYR 4 is the 2010 EPA IRIS Toxicological Review {U.S. EPA, 2010e, 5427469} (bolded in Table 6-1) because this is an EPA assessment that used the best available science in its evaluation of cancer risk, derivation of a cancer slope factor, and updated cancer classification for acrylamide. Although more recent health assessments were available, including a 2011 WHO GDWQ {WHO, 2011c, 11328275} and 2012 ATSDR Toxicological Profile {ATSDR, 2012b, 5926041}, the more recent health assessments did not derive either a TDI or CSF. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2010 EPA IRIS Toxicological Review derived a human cancer slope factor (central tendency) of 0.5 $(mg/kg/day)^{-1}$ based on a study by Johnson et al. (1986, 61340). In this study, F344 rats (90 rats/sex/treatment) were administered acrylamide in drinking water at calculated ingestion/body weight doses of 0, 0.01, 0.1, 0.5, or 2.0 mg/kg/day for 2 years. Increased incidences of thyroid tumors and tunica vaginalis mesotheliomas (TVMs) were observed in male rats. EPA used the rat benchmark dose lower confidence limit (BMDL) of 0.15 mg/kg/day as the POD from the critical effects of thyroid tumors or TVMs to derive the Human Equivalence Daily Intake of 0.194 mg/kg/day. The human oral slope factor of 0.51 $(mg/kg/day)^{-1}$ was derived by linear extrapolation from the HED to the origin, with background corrections.

The 2010 EPA IRIS assessment concluded that acrylamide is carcinogenic by a mutagenic mode of action and described acrylamide as "likely to be carcinogenic to humans," which corresponds to a cancer classification of L {U.S. EPA, 2010e, 5427469} according to EPA's current Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. Because acrylamide is classified as "likely to be

carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.1.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for acrylamide was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 8, 2022.

From this literature search, 1,882 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One-hundred and sixty-six of these 1,882 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,716 of the 1,882 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-2.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for acrylamide and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-2. Evidence Stream Heat Map Results for Acrylamide[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	784
Environmental Fate	–	303
Human	All	907
	Epidemiologic Quantitative Analyses	28
In Vitro	–	815
No Tag	–	166
Total Unique Studies		**1,716**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.1.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-3 shows the comparison of the basis for the existing and potential MCLGs for acrylamide.

Table 6-3. Comparison of the Basis for the Existing and Potential MCLGs for Acrylamide

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1991a, 5499)	Johnson et al. (1986, 61340)	Combination of tumor incidence data on mammary gland, thyroid, and uterus in female rats	3.7	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2010e, (5427469)	Johnson et al. (1986, 61340)	Thyroid tumors and tunica vaginalis mesotheliomas in male rats	0.5	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.1.5 SYR 4 Health Effects Conclusion

The existing NPDWR for acrylamide was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1991a, 5499}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2010 EPA IRIS Toxicological Review {U.S. EPA, 2010e, 5427469} to derive the potential MCLG because this is an EPA health assessment that used the best available science in its evaluation of cancer risk, derivation of a cancer slope factor, and updated cancer classification for acrylamide. Based on the analysis and conclusion presented in this health assessment, the CSF was set at 0.5 $(mg/kg/day)^{-1}$ and the cancer classification was updated to L, "likely to be carcinogenic to humans," according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For acrylamide, the more recent cancer descriptor of L would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.1.2 Antimony (CAS# 7440-36-0 | DTXSID5023879)

6.1.2.1 Basis of the Existing MCLG

EPA published the current NPDWR for antimony on July 17, 1992, establishing both an MCLG and an MCL of 0.006 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.0004 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991c, 758693}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.2.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The toxicity information used for SYR 4 is bolded in Table 6-4.

Table 6-4. Assessments Identified for Antimony

Chemical	Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
Antimony	EPA IRIS Chemical Assessment Summary {U.S. EPA, 1987f, 10328249}	0.0004	LOAEL	Schroeder et al. (1970, 68600)	–	–	–
	EPA OW Drinking Water Criteria Document {U.S. EPA, 1992h, 11311209}	0.0004	LOAEL	Schroeder et al. (1970, 68600)	–	–	–
	EPA OW Health Advisory {U.S. EPA, 1991c, 758693}	0.0004	LOAEL	Schroeder et al. (1970, 68600)	–	–	D[d]

Chemical	Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
	HC GDWQ {HC, 1999, 10528362}	0.0002	NOAEL	Poon et al. (1998, 749352)	–	–	–
	WHO GDWQ {WHO, 2003a, 758695}	0.006	NOAEL	Lynch et al. (1999, 749358); Poon et al. (1998, 749352)[e]	–	–	–
	CalEPA PHG {CalEPA, 2016a, 10489864}	**0.00014**	**$BMDL_{10}$**	**Poon et al. (1998, 749352)**	–	–	–
Antimony and Antimony Compounds	ATSDR Toxicological Profile {ATSDR, 1992a, 758696}	–[f]	–	–	–	–	–
	ATSDR Toxicological Profile {ATSDR, 2019a, 10536389}	0.0006[g]	NOAEL	Poon et al. (1998, 749352)	–	–	–
Soluble Antimony Compounds	EPA ORD PPRTV {U.S. EPA, 2008c, 1257804}	Refer to IRIS[h]	–	–	–	–	I[i]
Antimony Trioxide	EPA IRIS Chemical Assessment Summary {U.S. EPA, 1995, 10328128}[j]	–	–	–	–	–	–
	EPA ORD PPRTV {U.S. EPA, 2008d, 1257813}	0.5[k]	NOAEL	Hext et al. (1999, 749357)	–	–	I[i]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] Lynch et al. (1999, 749358) is a review article that reported a NOAEL that was different from Poon et al. (1998, 749352). The WHO GDWQ relied on the NOAEL determined by Lynch et al. (1999, 749358).

[f] Oral MRLs were not derived for any duration. Decreased lifespan was observed in rats at the lowest dose tested in the two available chronic oral studies {Schroeder, 1968, 626690; Schroeder, 1970, 68600}, but this health assessment concluded that there was no appropriate basis for a chronic-duration oral MRL.

[g] Intermediate-duration oral MRL; a chronic-duration oral MRL was not derived because the chronic oral database was considered inadequate.

[h] This health assessment defers to the 1987 EPA IRIS Chemical Assessment Summary for antimony {U.S. EPA, 1987f, 10328249}.
[i] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005, 10263976}.
[j] An oral RfD was not developed, and carcinogenicity was not evaluated in the IRIS Chemical Assessment Summary for antimony trioxide {U.S. EPA, 1995, 10328128}.
[k] Subchronic provisional RfD; a chronic provisional RfD was not derived for antimony trioxide because no chronic toxicity data were available, and the health assessment states that adding an additional UF of 10 for subchronic-to-chronic duration would result in a composite UF of 10,000, which would exceed EPA's maximum-allowed UF of 3,000.

The health assessment selected for SYR 4 is the 2016 CalEPA PHG {CalEPA, 2016a, 10489864} (bolded in Table 6-4) because it uses a more current modeling approach compared to other health assessments of antimony (e.g., the 2019 ATSDR Toxicological Profile uses a NOAEL approach), resulting in a more health protective POD. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2016 CalEPA PHG derives an RfD for antimony based on Poon et al. (1998, 749352). This 90-day subchronic oral toxicity study in Sprague-Dawley rats evaluated the effects of antimony exposure via drinking water. Rats were exposed to antimony potassium tartrate (a soluble trivalent antimony salt) in the drinking water at concentrations of 0, 0.5, 5, 50, or 500 ppm for 90 days. At 5 ppm and above, histological and biochemical changes in several tissues were observed. Blood glucose level changes and tissue retention of antimony at 5 ppm and above were considered by CalEPA as additional supportive evidence of antimony toxicity. No effects were seen in the 0.5 ppm group, a dose level that was equivalent to a calculated average intake of 0.06 mg/kg/day {Poon, 1998, 749352}. CalEPA subsequently used BMD modeling to derive the toxicity value for antimony using the data from Poon et al. (1998, 749352). CalEPA selected a histopathological change in liver (i.e., liver nuclear anisokaryosis) in male rats as the critical effect to perform BMD modeling and selected the benchmark dose lower limit ($BMDL_{10}$) of 0.14 mg/kg/day as the POD {CalEPA, 2016a, 10489864}. A total uncertainty factor (UF) of 1,000 was then applied to this POD: 10 for interspecies variability, 30 for intraspecies variability, and 3 for extrapolation from subchronic to chronic exposure. CalEPA applied a UF of 30 for intraspecies variability due to concerns that a UF of 10 (the typical EPA maximum for this UF) would not be sufficient to protect infants and children {CalEPA, 2016a, 10489864; CalEPA, 2008, 193231}. After applying the total UF, the oral RfD for antimony was calculated to be 0.00014 mg/kg/day or 0.14 µg/kg/day.

The CalEPA PHG does not assign a cancer descriptor; therefore, EPA referred to the EPA OW Health Advisory {U.S. EPA, 1991c, 758693} for the cancer descriptor, which was determined to be Group D, "not classifiable as to human carcinogenicity" according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on inconclusive evidence regarding the potential carcinogenicity of antimony when ingested in drinking water.

6.1.2.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the 2019 ATSDR Toxicological Profile was used to assign the date limit {ATSDR, 2019a, 10536389}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for antimony was defined as one year prior to January 2018, resulting in a search date range from January 1, 2017 to January 24, 2022.

From this literature search, 966 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Forty-seven of these 966 unique studies were categorized to an evidence stream not used for this

project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 919 of the 966 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-5.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for antimony and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-5. Evidence Stream Heat Map Results for Antimony[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	152
Environmental Fate	–	421
Human	All	434
	Epidemiologic Quantitative Analyses	36
In Vitro	–	224
No Tag	–	71
Total Unique Studies		**919**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.2.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-6 shows the comparison of the basis for the existing and potential MCLGs for antimony.

Table 6-6. Comparison of the Basis for the Existing and Potential MCLGs for Antimony

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992g, 10587719)	–	–	–	D	–	–	–	–	–	–
EPA (1991c, 758693)	Schroeder et al. (1970, 68600)	Decreased longevity, decreased blood glucose, and increased blood cholesterol	–	–	0.0004	40%	General Population	70 kg adult, 2 L/day	0.006	–
Relevant Health Assessments Identified in SYR 4										
EPA (1991c, 758693)	–	–	–	D	–	–	–	–	–	–
CalEPA (2016a, 10489864)	Poon et al. (1998, 749352)	Histopathological changes in rat liver	–	–	0.00014	40%	General Population	33.8 mL/kg/ day	–	0.002

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.2.5 SYR 4 Health Effects Conclusion

The existing NPDWR for antimony was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.0004 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 40%, EPA set the MCLG at 0.006 mg/L and assigned antimony a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991c, 758693}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the CalEPA PHG {CalEPA, 2016a, 10489864} to derive the potential MCLG because its toxicity value is based on a more recent critical study than the most recent EPA health assessment for antimony {U.S. EPA, 1995, 10328128} and because it uses a more current modeling approach. Based on an RfD of 0.00014 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 40%, EPA calculated a potential MCLG of 0.002 mg/L. The CalEPA PHG did not assign a cancer descriptor; therefore, EPA defaulted to the EPA OW Health Advisory cancer descriptor of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991c, 758693}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.006 mg/L to 0.002 mg/L.

6.1.3 Barium (CAS# 7440-39-3 | DTXSID8023894)

6.1.3.1 Basis of the Existing MCLG

EPA published the current NPDWR for barium on July 1, 1991, establishing both an MCLG and an MCL of 2 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.07 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA 1990b, 10709982} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.3.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity for barium that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-7.

Table 6-7. Assessments Identified for Barium

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985c, 10509464}	0.05	LOAEL	Perry et al. (1973, 10520114)	–	–	–
HC GDWQ {HC, 1990, 10524697}	–	–	–	–	–	–[d]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990b, 10709982}	0.07	NOAEL	Wones et al. (1990, 10480483)	–	–	D[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1993a, 10509466}	0.07	NOAEL	Wones et al. (1990, 10480483)	–	–	D[e]
EPA IRIS Toxicological Review {U.S. EPA, 2005c, 11311280}[f]	0.2	$BMDL_{05}$	NTP (1994, 4517491)	–	–	N[g]
CalEPA PHG {CalEPA, 2003a, 10489842}	**0.067[h]**	**NOAEL**	**Brenniman and Levy (1984, 10510387)**	–	–	–
ATSDR Toxicological Profile {ATSDR, 2007a, 669580}	0.2	NOAEL	NTP (1994, 4517491)	–	–	–
WHO GDWQ {WHO, 2016a, 10509460}	0.21[i]	$BMDL_{05}$	NTP (1994, 4517491)	–	–	–
HC GDWQ {HC, 2020a, 10529367}	0.19[i]	$BMDL_{05}$	NTP (1994, 4517491)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; $BMDL_{05}$ = benchmark dose level at the 95% lower confidence limit on a 5% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the maximum acceptable concentration (MAC), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Classified as Group VA (inadequate data for evaluation) by HC.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] Oral RfD revised in 2005; carcinogenicity assessment revised in 1998.

[g] Based on EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}, barium is considered "not likely to be carcinogenic to humans."

[h] POD/UF calculated based on a POD of 0.20 mg/kg/day and a total UF of 3.

[i] TDI based on increased incidence of nephropathy in male mice.

The health assessment selected for SYR 4 is the 2005 EPA IRIS Toxicological Review (2005c, 11311280) (bolded in Table 6-7) because it is an EPA health assessment that derives an oral toxicity value and uses the best available science in its evaluation of non-cancer risk. Although more current health assessments were available, including the ATSDR Toxicological Profile (2007a, 669580), WHO GDWQ (2016a, 10509460), and HC GDWQ (2020a, 10529367), those health assessments did not introduce new science (e.g., the toxicity value was not based on a newer critical study) or use updated methodologies for deriving the POD compared to the 2005 EPA IRIS Toxicological Review (2005c, 11311280). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the 2005 EPA IRIS Toxicological Review (2005c, 11311280), EPA chose a 2-year toxicity study {NTP, 1994, 4517491} to derive a POD for the chronic oral RfD. In this study, B6C3F1 mice (60 animals/sex/group) were exposed to barium chloride dihydrate in drinking water at concentrations of

0, 500, 1,250, or 2,500 ppm for 2 years. Nephropathy was observed in exposed mice of both sexes relative to control animals; lesions were characterized by renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and crystals in the lumen of the renal tubules {NTP, 1994, 4517491}. Nephropathy was chosen as the critical effect. The chronic oral RfD was derived using BMD modeling to calculate the benchmark dose lower limit on a 5% response ($BMDL_{05}$). The $BMDL_{05}$ values for male and female mice were similar, but because there was slightly less uncertainty in the estimated value derived from male mice compared to female mice, the $BMDL_{05}$ for renal lesions in male mice (63 mg/kg/day) was used to derive an RfD. A total UF of 300 was applied to the POD: 10 for interspecies variability, 10 for intraspecies variability, and 3 for database deficiencies. After applying the total UF, the chronic oral RfD was calculated to be 0.2 mg/kg/day.

Based on available evidence from animal studies, the 2005 EPA IRIS Chemical Assessment Summary concluded that barium is "not likely to be carcinogenic to humans" {EPA, 2005e, 10535247} according to EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}.

6.1.3.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For SYR 4, barium was subject to both a standard and a targeted literature search. The HC GDWQ health assessment was used to assign the date limit for the standard search {HC, 2020a, 10529367}. The start date of the SYR 4 standard literature search conducted in PubMed and Web of Science for barium was defined as one year prior to January 2020, resulting in a search date range from January 1, 2019 to March 23, 2022.

From this literature search, 488 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty-two of these 488 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 466 of the 488 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-8.

Table 6-8. Evidence Stream Heat Map Results for Barium[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	117
Environmental Fate	–	131
Human	All	281
	Epidemiologic Quantitative Analyses	26
In Vitro	–	131
No Tag	–	39
Total Unique Studies		**466**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

For barium, there was specific interest in capturing studies published between 2007 and 2019 that evaluated hearing effects and developmental and reproductive toxicity. These health effects were not specifically searched for in SYR 3; therefore, a targeted search date for barium was pushed back to 2007, prior to the publication of the SYR 3, to ensure studies on these outcomes were identified. The targeted search was conducted from January 2007 to January 2019, covering the time between the ATSDR Toxicological Profile conducted in 2007, which was the next most recent health assessment after the 2005 EPA IRIS Chemical Assessment Summary, and the 2020 HC GDWQ.

From this literature search, 538 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty of these 538 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 518 of the 538 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-9.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for barium and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-9. Evidence Stream Heat Map Results for Barium Hearing Effects and Developmental Reproductive Toxicity Targeted Search[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	130
Environmental Fate	–	53
Human	All	398
	Epidemiologic Quantitative Analyses	35
In Vitro	–	109
No Tag	–	29
Total Unique Studies		**518**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.3.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6 10 shows the comparison of the basis for the existing and potential MCLGs for barium.

Table 6-10. Comparison of the Basis for the Existing and Potential MCLGs for Barium

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990b, 10709982)	–	–	–	D	–	–	–	–	–	–
EPA (1990b, 10709982)	Wones et al. (1990, 10480483)	Absence of a hypertensive effect in humans	–	–	0.07	100%[d]	General Population	70 kg adult, 2 L/day	2	–
Relevant Health Assessment Identified in SYR 4										
EPA (2005c, 11311280)	–	–	–	N	–	–	–	–	–	–
EPA (2005c, 11311280)	NTP (1994, 4517491)	Nephropathy in 2-yr drinking water study in mice	–	–	0.2	80%[e]	General Population	33.8 mL/ kg/day	–	5.6

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] EPA did not apply an RSC because the basis for the RfV is a human study in which contributions from food and air were considered {U.S. EPA, 1991a, 5499}.

[e] An RSC of 80% was determined using the Exposure Decision Tree approach described in the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health {U.S. EPA, 2000c, 19428}. The dietary component of the RSC estimate was based on data from the United Kingdom Total Diet Study and not on data from the United States. Dietary data for the United States are not available. The diet in the United Kingdom is relatively consistent with that in the United States and qualifies for use in the RSC analysis {U.S. EPA, 2016c, 6557097}.

6.1.3.5 SYR 4 Health Effects Conclusion

The existing NPDWR for barium was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.07 mg/kg/day {U.S. EPA 1990b, 10709982}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 100%, EPA set the MCLG at 2 mg/L and assigned barium a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA 1990b, 10709982}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2005 EPA IRIS Toxicological Review (2005c, 11311280) to derive the potential MCLG because it is an EPA health assessment that derives an oral toxicity value and uses the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.2 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 80% {U.S. EPA, 2016c, 6557097}, EPA calculated a potential MCLG of 5.6 mg/L. Based on the analysis and conclusion presented in this health assessment, the cancer classification was updated to N, "not likely to be carcinogenic to humans," in accordance with the 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}. EPA concluded that new health effects information supports raising the current MCLG of 2 mg/L to the potential MCLG of 5.6 mg/L.

6.1.4 Benzene (CAS# 71-43-2 | DTXSID3039242)

6.1.4.1 Basis of the Existing MCLG

EPA published the current NPDWR for benzene on July 8, 1987{U.S. EPA, 1987m, 3809376}. The NPDWR established an MCLG of zero based on EPA's classification of benzene as a known "human carcinogen" (Group A) {U.S. EPA, 1985d, 3809374} according to EPA's 1984 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1984a, 33496} (see Table 3-1 for more information on cancer classification). The NPDWR established an MCL of 0.005 mg/L, based on the practical quantitation limit {U.S. EPA, 1987m, 3809376}.

6.1.4.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity for benzene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-11.

Table 6-11. Assessments Identified for Benzene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985e, 10509477}	0.0007[d]	NOAEL	Wolf et al. (1956, 62279)	–	–	–
	0.002[d]	NOAEL	Chang (1972, 10519032); Doskin (1971, 10519329)			
EPA OW Health Advisory {U.S. EPA, 1987g, 5427439}	–[e]	–	–	–	–	A[f]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG {CalEPA, 2001a, 5426179}	0.0087[g]	NOAEL	Tsai et al. (1983, 628632)	0.1	Paxton et al. (1994a, 192966; 1994b, 192967); Hayes et al. (1997, 646303)	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2003e, 5176611}	0.004[h]	BMDL	Rothman et al. (1996, 80360)	**0.015 to 0.055**	**Rinsky et al. (1981, 32312; 1987, 32313); Paustenbach et al. (1993, 2955460); Crump (1994, 674880); EPA (1998c, 93089; 1999b, 2344809)**	**A[f]**
WHO GDWQ {WHO, 2003b, 10509426}	–	–	–	–	–	–
ATSDR Toxicological Profile, ATSDR Addendum {ATSDR, 2015a, 10489753}[i]	0.0005[j]	$BMDL_{0.25sdADJ}$	Lan et al. (2004a, 628629; 2004b, 10571017)	–[k]	–	–[k]
HC GDWQ {HC, 2009, 5432332}	–[l]	–	–	–[m]	–	–
EPA ORD PPRTV {U.S. EPA, 2009c, 1257817}	Refer to IRIS	–	–	Refer to IRIS	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; BMDL = benchmark dose 95% lower confidence limit; $BMDL_{0.25sdADJ}$ = benchmark dose 95% lower confidence limit associated with 0.25 standard deviation from the control value, adjusted for continuous exposure.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment provides two different adjusted ADI values and does not indicate which is the preferred oral reference value. One value is based on an oral exposure study in rats {Wolf, 1956, 62279} with a NOAEL of 1 mg/kg, multiplied by a factor of 5/7 to adjust for five days of dosing per week, and divided by a total UF of 1,000. The other value is based on human occupational studies of inhalation exposure {Chang, 1972, 10519032; Doskin, 1971, 10519329} in which an average daily intake of 0.153 mg/day was calculated using a NOAEL of 10 ppm and a total UF of 1,000.

[e] Longer-term and lifetime Health Advisories were not derived because of the known carcinogenic potential of benzene.

[f] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[g] This value is the POD/UF calculated from a NOAEL of 0.087 mg/kg/day and a total UF of 10. This health assessment reported that the inhalation NOAEL of 0.53 ppm was converted to an equivalent oral dose in mg/kg/day for use as the POD by first

adjusting the value from an occupational exposure to a continuous population exposure concentration of 0.19 ppm, and then converting to mg/kg/day using the following formula:
0.19 × (3,190 µg/m^3 air/ppm) × (1/70 kg) × (20 m^3/day) × (0.5 absorbed) × (mg/1000 µg) where 3190 µg/m^3 air is equivalent to 1 ppm benzene, 70 kg is a standard adult male body weight value, 20 m^3/day is the default value for volume of air inhaled, 0.5 is the value for benzene absorption efficiency (50%) for inhalation (reportedly estimated from the available literature), and 100% absorption was assumed for oral ingestion (also reportedly estimated from the literature).

[h] As reported in the EPA IRIS Chemical Assessment Summary, the BMDL that was used as the POD for this oral reference value was derived from the inhalation $BMCL_{ADJ}$ (the 95% lower bound on the benchmark concentration, adjusted for continuous exposure) of 8.2 mg/m^3 as follows: 8.2 mg/m^3 × 20 m^3/day × 0.5 ÷ 70 kg = BMDL of 1.2 mg/kg/day, where 70 kg is a standard adult male body weight value, 20 m^3/day is the default human ambient volume of air inhaled in a 24-hour day, and 0.5 is the assumed value for inhalation absorption efficiency (50%); oral absorption was assumed to be 100% in the dose range near the benchmark concentration.

[i] Toxicological Profile was originally published in 2007 {ATSDR, 2007b, 684206} and an addendum was published in 2015 {ATSDR, 2015a, 10489753}.

[j] MRL derived for chronic-duration oral exposure (365 days or more) to benzene; the inhalation $BMCL_{0.25sdADJ}$ (benchmark concentration 95% lower confidence limit associated with 0.25 standard deviation from the control value, adjusted for continuous exposure) was converted to an equivalent $BMDL_{0.25sdADJ}$ for use as the POD.

[k] This health assessment reports the CSF range and the cancer classification determined by the EPA IRIS Chemical Assessment Summary {U.S. EPA, 2003e, 5176611}.

[l] The HC GDWQ for benzene is based on carcinogenic effects; this health assessment does not report an oral reference value or CSF.

[m] This health assessment defers to the EPA IRIS Chemical Assessment Summary for benzene {U.S. EPA, 2003e, 5176611}.

The health assessment selected for SYR 4 is the 2003 EPA IRIS Chemical Assessment Summary {U.S. EPA, 2003e, 5176611} (bolded in Table 6-11) because it is the most recent EPA health assessment that evaluates cancer risk via oral exposure, derived a cancer slope factor, and designated a cancer descriptor for benzene. Although more recent health assessments were available, including an ATSDR Toxicological Profile and ATSDR Addendum {ATSDR, 2007b, 684206; ATSDR, 2015a, 10489753}, HC GDWQ {HC, 2009, 5432332}, and EPA ORD PPRTV {U.S. EPA, 2009c, 1257817}, these health assessments did not derive a cancer slope factor. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

As noted in the 2003 EPA IRIS Chemical Assessment Summary, several occupational inhalation studies {Rinsky, 1981, 32312; Rinsky, 1987, 32313; Paustenbach, 1993, 2955460; Crump, 1994, 674880; U.S. EPA, 1998c, 93089; U.S. EPA, 1999b, 2344809} served as the basis for the inhalation unit risk range for benzene, which was then subsequently extrapolated to an oral slope factor based on elevated hematologic cancer risk associated with benzene inhalation. An inhalation unit risk range of 2.2×10^{-6} to 7.8×10^{-6} per µg/m^3 for benzene in air was derived from human occupational data for leukemia. This range was extrapolated to an oral CSF of 1.5×10^{-2} to 5.5×10^{-2} per mg/kg/day, by assuming a standard air intake of 20 m^3/day, a standard body weight of 70 kg for an adult human, and 50% absorption via inhalation.

According to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA classifies benzene as a known "human carcinogen" for all routes of exposure based on evidence from epidemiological studies and case studies as well as supporting evidence from animal studies {U.S. EPA, 2003e, 517661}. Because benzene is classified as a known "human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.4.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA Six-Year Review Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for benzene was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 4, 2022.

From this literature search, 3,980 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Three-hundred and ten of these 3,980 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 3,670 of the 3,980 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-12.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for benzene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-12. Evidence Stream Heat Map Results for Benzene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	687
Environmental Fate	–	1,283
Human	All	1,958
	Epidemiologic Quantitative Analyses	381
In Vitro	–	1,090
No Tag	–	444
Total Unique Studies		**3,670**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.4.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-13 shows the comparison of the basis for the existing and potential MCLGs for benzene.

Table 6-13. Comparison of the Basis for the Existing and Potential MCLGs for Benzene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987m, 3809376)	–	–	–	A	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2003e, 5176611)	Rinsky et al. (1981, 32312; 1987, 32313); Paustenbach et al. (1993, 2955460); Crump (1994, 674880); EPA (1998c, 93089; 1999b, 2344809)	Leukemia	0.015 to 0.055	A	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.4.5 SYR 4 Health Effects Conclusion

The existing NPDWR for benzene was published on July 8, 1987{U.S. EPA, 1987m, 3809376}. Based on a cancer classification of A, known "human carcinogen" {U.S. EPA, 1985d, 3809374} according to EPA's 1984 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1984a, 33496}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2003 EPA IRIS Chemical Assessment Summary {U.S. EPA, 2003e, 5176611} to derive the potential MCLG because it is the most recent EPA health assessment that derived an oral cancer slope factor for benzene. Based on the analysis and conclusion presented in the 2003 EPA IRIS Chemical Assessment Summary, the cancer classification for benzene was maintained at A, known "human carcinogen." For benzene, more recent information does not support a change to the MCLG.

6.1.5 Benzo(a)pyrene (CAS# 50-32-8 | DTXSID2020139)

6.1.5.1 Basis of the Existing MCLG

EPA published the current NPDWR for benzo(a)pyrene on July 17, 1992 {U.S. EPA, 1992g, 10587719}, establishing an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1991d, 1012038} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.0002 mg/L, based on analytical feasibility {U.S. EPA, 1992g, 10587719}.

6.1.5.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for benzo(a)pyrene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-14.

Table 6-14. Assessments Identified for Benzo(a)pyrene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1991d, 1012038}	–[d]	–	–	5.79[e]	Neal and Rigdon (1967, 60096); Brune et al. (1981, 1012348)	B2[f]
ATSDR Toxicological Profile {ATSDR, 1995, 625705}	–[g]	–	–	–[g]	–	–[h]
WHO GDWQ {WHO, 2003c, 10509433}	–[i]	–	–	–[i]	–	–
CalEPA PHG {CalEPA, 2010c, 1254299}	0.0017	LOAEL	Knuckles et al. (2001, 1012145)	2.9	Culp et al. (1998, 1012242)	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
HC GDWQ {HC, 2016, 10529368}	0.0000667	NOAEL	Chen et al. (2012, 1010779)	1.289	Culp et al. (1998, 1012242); Moffat et al. (2015, 2947764)	–
EPA IRIS Toxicological Review {U.S. EPA, 2017e, 3839268}	0.0003	$BMDL_{1SD}$	Chen et al. (2012, 1010779)	1	**Culp et al. (1998, 1012242)**	**H[j]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; $BMDL_{1SD}$ = benchmark dose 95% lower confidence limit associated with 1 standard deviation from the control value.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), acceptable daily dose (ADD), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment did not derive an oral RfD for benzo(a)pyrene because the available data showed that the appearance of neoplastic effects occurred at lower doses than did indicators of systemic toxicity.

[e] This health assessment derived nine candidate cancer slope factors and noted that each candidate CSF is based on a "less-than-optimal but acceptable data set" and that "there is little basis on which to make a recommendation of a single slope factor from [the candidate slope factors]." The assessment excluded "estimates considered inappropriate," and the CSF of 5.79 $(mg/kg/day)^{-1}$ represents the geometric mean of the remaining four slope factors from "the most acceptable data sets" (range 4.5–9.0 $(mg/kg/day)^{-1}$).

[f] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[g] This health assessment did not derive an MRL or CSF for benzo(a)pyrene; no chronic oral MRLs were derived for polycyclic aromatic hydrocarbons because there are no adequate human or animal dose-response data available that identify threshold values for appropriate noncancer health effects. Intermediate-duration oral MRLs were only derived for acenaphthene (0.6 mg/kg/day), anthracene (10 mg/kg/day), fluoranthene (0.4 mg/kg/day), and fluorene (0.4 mg/kg/day).

[h] This health assessment reports that EPA determined that benzo(a)pyrene is a probable human carcinogen (citation not provided).

[i] This health assessment did not derive a TDI or CSF for benzo(a)pyrene; a guideline value for benzo(a)pyrene corresponding to an excess lifetime cancer risk of 10^{-5} was estimated as 0.7 µg/L based on data from Neal and Rigdon (1967, 60096).

[j] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2017 IRIS Toxicological Review of Benzo(a)pyrene {U.S. EPA, 2017e, 3839268} (bolded in Table 6-14) because it is the most recently published EPA health assessment that derives an oral toxicity value, a cancer descriptor following EPA's current, 2005 Cancer Guidelines {U.S. EPA, 2005d, 10263976}, and used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for benzo(a)pyrene using BMD modeling. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals).

In this health assessment, EPA selected a two-year chronic study in female B6C3F1 mice {Culp et al., 1998, 1012242} as the critical study for dose-response analysis and linear extrapolation of cancer risk. Mice (40/dose) were exposed to 0, 5, 25, or 100 ppm in the diet (estimated to be equivalent to 0, 0.7, 3.3, and 16.5 mg/kg/day, respectively) and increased incidences of forestomach, esophagus, tongue, and larynx tumors were observed in exposed female mice. EPA used the benchmark dose lower confidence limit (BMDL) of 0.071 mg/kg/day based on the alimentary tract tumor response as the POD to derive the human equivalent dose (HED) using $(body\ weight)^{3/4}$ scaling (the default approach for interspecies extrapolation when the dose metric is not an area under the curve). An oral slope factor of 1 $(mg/kg/day)^{-1}$ was derived using the multistage-Weibull model {U.S. EPA, 2017e, 3839268}.

Following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA determined that benzo(a)pyrene is "carcinogenic to humans" based on strong, consistent evidence of carcinogenicity in animals and humans via all administration routes {U.S. EPA, 2017e, 3839268}. Because benzo(a)pyrene is classified as "carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.5.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for benzo(a)pyrene was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 8, 2022. From the literature searches performed, a total of 2,529 unique studies were identified following review of the literature. Following SWIFT-Review, 2,449 of the 2,529 unique studies were tagged to the evidence stream categories shown in Table 6-15.

From this literature search, 2,529 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Eighty of these 2,529 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 2,449 of the 2,529 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-15.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for benzo(a)pyrene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-15. Evidence Stream Heat Map Results for Benzo(a)pyrene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,117
Environmental Fate	–	738
Human	All	1,452
	Epidemiologic Quantitative Analyses	92
In Vitro	–	1,268
No Tag	–	86
Total Unique Studies		**2,449**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.5.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-16 shows the comparison of the basis for the existing and potential MCLGs for benzo(a)pyrene.

Table 6-16. Comparison of the Basis for the Existing and Potential MCLGs for Benzo(a)pyrene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1991d, 1012038)	Neal and Rigdon (1967, 60096); Brune et al. (1981, 1012348)	Gastric tumors	5.79	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2017e, 3839268)	Beland and Culp (1998, 1012027)	Alimentary tract tumors	1	H	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.5.5 SYR 4 Health Effects Conclusion

The existing NPDWR for benzo(a)pyrene was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1991d, 1012038} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2017 IRIS Toxicological Review of Benzo(a)pyrene {U.S. EPA, 2017e, 3839268} to derive the potential MCLG because it is the most recently published EPA health assessment that derives an oral toxicity value and used the best available science. Based on the analysis and conclusion presented in this health assessment, a CSF of 1.0 $(mg/kg/day)^{-1}$ was derived and the cancer descriptor was updated to H, "carcinogenic to humans" by all routes of exposure according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For benzo(a)pyrene, the more recent cancer descriptor of H would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.1.6 Beryllium (CAS# 7440-41-7 | DTXSID4023913)

6.1.6.1 Basis of the Existing MCLG

EPA published the current NPDWR for beryllium on July 17, 1992, establishing both an MCLG and an MCL of 0.004 mg/L {U.S. EPA, 1992g, 10587719}. EPA classified beryllium in Group B2, "probable human carcinogen," based on clear evidence of its carcinogenicity via inhalation or injection in several animal species {U.S. EPA, 1991d, 1272707} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. At the time of promulgation, EPA used a three-category approach for establishing MCLGs that was based on evidence of carcinogenicity via drinking water. Using this "MCLG Three Category Approach," EPA determined that beryllium was a Category II drinking water contaminant based on "limited evidence considering weight of evidence, pharmacokinetics, potency and exposure" (see Section 3.1.2.1 for more information on the MCLG Three Category Approach). As such, EPA used the RfD approach to apply an added risk management safety factor of 10 {U.S. EPA, 1992g, 10587719} to derive the MCLG of 0.004 mg/L from the RfD of 0.005 mg/kg/day {U.S. EPA, 1991e, 1272707} to account for possible carcinogenicity {U.S. EPA, 1992g, 10587719} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.1.6.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for beryllium that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-17.

Table 6-17. Assessments Identified for Beryllium

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1991e, 1272707}	0.005	NOAEL	Schroeder and Mitchener (1975, 8916)	4.3	Schroeder and Mitchener (1975, 8916)	B2[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1998b, 999207}	**0.002[e]**	**$BMDL_{10}$**	**Morgareidge et al. (1976, 5935664)**	**–**	**–**	**–[d,f]**
ATSDR Toxicological Profile; Addendum {ATSDR, 2002a, 1269287; 2015b, 10489756}	0.002[e]	$BMDL_{10}$	Morgareidge et al. (1976, 5935664)	–	–	–
CalEPA PHG {CalEPA, 2003b, 10489843}	0.00015[e,g]	NOAEL[h]	Morgareidge et al. (1976, 5935664)	–	–	–
WHO GDWQ {WHO, 2009a, 10509455}	0.002[e]	$BMDL_{10}$	Morgareidge et al. (1976, 5935664)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] Based on small intestine lesions in dogs chronically exposed to beryllium in diet (as beryllium sulfate tetrahydrate).

[f] This characterization describes the human carcinogenic potential of inhaled beryllium. Data for the oral route were considered "inadequate for assessing the carcinogenic potential of ingested beryllium" {U.S. EPA, 1998b, 999207}.

[g] POD/UF calculated based on a POD of 0.15 mg/kg/day and a total UF of 1000.

[h] CalEPA (2003b, 10489843) determined the NOAEL from Morgareidge et al. (1976, 5935664) to be 0.15 mg/kg/day. CalEPA also performed BMD modeling of the critical endpoint of small intestine lesions from this study and calculated a $BMDL_{05}$ (benchmark dose level at the 95% lower confidence limit on a 5% response) of 0.2 mg/kg/day.

The health assessment selected for SYR 4 is the EPA IRIS Chemical Assessment Summary (1998b, 999207) (shown bolded in Table 6-17) because this is an EPA assessment that used the best available science and a more current modeling approach (i.e., BMD modeling) for dose-response characterization than other health assessments, resulting in a more health protective POD. Although more recent health assessments were available, including the ATSDR Toxicological Profile (2002a, 1269287), CalEPA's PHG (2003b, 10489843), and WHO GDWQ (2009a, 10509455), these health assessments did not introduce new science (e.g., the toxicity value was not based on a newer critical study). Although CalEPA's PHG derived a lower RfD of 0.00015 mg/kg/day {CalEPA, 2003b, 10489843}, this health assessment used a NOAEL modeling approach instead of the updated BMD approach used in the 1998 EPA IRIS Chemical Assessment Summary. Furthermore, the more recent 2009 WHO GDWQ {WHO, 2009a, 10509455} derived the same RfD using a modeling approach similar to that used in the 1998 IRIS Chemical Assessment Summary. All of the identified assessments postdating 1998 used the same critical study {Morgareidge et al., 1976, 5935664}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 1998 IRIS Chemical Assessment selected a study of beagle dogs {Morgareidge et al., 1976, 5935664}, aged 8–12 months (5/sex/treatment), fed diets containing 0, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate for 172 weeks as the critical study. Dose-related development of gastrointestinal lesions, the critical effect, was observed. A benchmark dose lower confidence limit ($BMDL_{10}$) of 0.46 mg/kg/day was derived based on small intestinal lesions in male dogs. A total uncertainty factor (UF) of 300 was applied to the $BMDL_{10}$: 10 for interspecies variability and 10 for intraspecies variability, and 3 for database deficiencies due to the lack of human toxicity data via the oral route and inadequate assessment of reproductive/developmental and immunotoxicologic endpoint data in animals. After applying the total UF to the $BMDL_{10}$, the oral RfD was calculated to be 0.002 mg/kg/day.

Based on the weight of evidence (limited human and sufficient animal data), beryllium was classified as a "probable human carcinogen" (B1) {U.S. EPA, 1998b, 999207} according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. However, this characterization describes the human carcinogenic potential of inhaled beryllium. Limited carcinogenicity data is available, and the evidence base is therefore considered "inadequate for assessing the carcinogenic potential of ingested beryllium" {U.S. EPA, 1998, 999207} according to EPA's proposed 1996 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}.

6.1.6.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for beryllium was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to February 23, 2022.

From this literature search, 318 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Fifteen of these 318 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 303 of the 318 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-18.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for beryllium and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-18. Evidence Stream Heat Map Results for Beryllium[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	34
Environmental Fate	–	95
Human	All	195
	Epidemiologic Quantitative Analyses	49
In Vitro	–	54
No Tag	–	32
Total Unique Studies		**303**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.6.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-19 shows the comparison of the basis for the existing and potential MCLGs for beryllium.

Table 6-19. Comparison of the Basis for the Existing and Potential MCLGs for Beryllium

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Oral Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1991e, 1272707)	Schroeder and Mitchener (1975, 8916)	Statistically nonsignificant increase in the incidence of lymphoma leukemia in female mice and slightly higher but still nonsignificant increase in the incidence of grossly observed tumors in male rats	4.3	B2	–	–	–	–	–	–
EPA (1991e, 1272707)	Schroeder and Mitchener (1975, 8916)	Slight reduction in body weight in male rats (absence of other effects in rats)	–	–	0.005	20%	General Population	–	0.004[d]	–
Relevant Health Assessment Identified in SYR 4										
EPA (1998b, 999207)	–	–	–	[e]	–	–	–	–	–	–
EPA (1998b, 999207)	Morgareidge et al. (1976, 5935664)	Small intestine lesions in dogs	–	–	0.002	20%	General Population	33.8 mL/ kg/day	–	0.01[f]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] EPA placed beryllium in drinking water Category II for regulation based on the weight of evidence for carcinogenicity via ingestion, and the potency, exposure, and pharmacokinetics of this chemical. This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity {U.S. EPA, 1991e, 1272707}.

[e] EPA designated beryllium as B1 "probable human carcinogen, based on the limited evidence of carcinogenicity in humans exposed to airborne beryllium (lung cancer) and sufficient evidence of carcinogenicity in animals (lung cancer in rats and monkeys inhaling beryllium, lung tumors in rats exposed to beryllium via intratracheal instillation, and

osteosarcomas in rabbits and possibly mice receiving intravenous or intramedullary injection)." Data for oral route were considered "inadequate for assessing the carcinogenic potential of ingested beryllium" {U.S. EPA, 1998b, 999207}.

[f] EPA placed beryllium in drinking water Category III based on inadequate data to determine the human carcinogenic potential of ingested beryllium, according to the 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524; U.S. EPA, 1998b, 999207}. Therefore, the SYR 4 potential MCLG is derived using the RfD approach without an additional risk management safety factor.

6.1.6.5 SYR 4 Health Effects Conclusion

The existing NPDWR for beryllium was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.005 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.004 mg/L and assigned beryllium a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1992g, 10587719}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity {U.S. EPA, 1992g, 10587719} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor). Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1998b, 999207} to derive the potential MCLG because this is an EPA health assessment that used the best available science and a more current modeling approach (i.e., BMD modeling) for dose-response characterization, resulting in a more health protective POD. Based on the analysis of and conclusion about inhalation data presented in this 1998 IRIS Chemical Assessment Summary, EPA updated the cancer classification to B1, "probable human carcinogen," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The 1998 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1998b, 999207} states that inhaled beryllium would be characterized as a "likely" carcinogen, but that the human carcinogenic potential of ingested beryllium cannot be determined because of inadequate data based on EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}. The 1998 EPA assessment determined that beryllium was a Category III drinking water contaminant based on "inadequate or no animal evidence" due to a lack of data pertaining to human carcinogenic potential of ingested beryllium. Therefore, the SYR 4 potential MCLG is derived using the RfD approach without an additional risk management safety factor {U.S. EPA, 1991e, 1272707; U.S. EPA, 1996a, 83524; U.S. EPA, 1998b, 999207}. Based on an RfD of 0.002 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20% {U.S. EPA, 2016c, 6557097}, EPA calculated a potential MCLG of 0.01 mg/L. EPA concluded that the new health effects information supports raising the current MCLG of 0.004 mg/L to the potential MCLG of 0.01 mg/L.

6.1.7 Cadmium (CAS# 7440-43-9 | DTXSID1023940)

6.1.7.1 Basis of the Existing MCLG

EPA published the current NPDWR for cadmium on January 30, 1991, establishing both an MCLG and an MCL of 0.005 mg/L {U.S. EPA, 1991a, 5499}. Because of inadequate dose-response data to characterize the carcinogenic hazard from oral exposure, EPA classified cadmium as a Group D carcinogen, "not classifiable as to human carcinogenicity" by the oral route of exposure {U.S. EPA, 1991a, 5499}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). EPA derived the MCLG for cadmium based on the RfD of 0.0005 mg/kg/day {U.S. EPA, 1986b, 199114} for human renal dysfunction {U.S. EPA, 1991a, 5499}.

6.1.7.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for cadmium that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-20.

Table 6-20. Assessments Identified for Cadmium

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1986b, 199114}	0.0005	LOAEL	Friberg et al. (1974, 9282)	–	–	–
HC GDWQ {HC, 1986, 10634789}	–[d]	–	–	–	–	–
EPA OW Health Advisory {U.S. EPA, 1987h, 10606112}	0.0005	LOAEL	Friberg et al. (1974, 9282)	–	–	D[e]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989b, 10605332}[f]	0.0005[g]	NOAEL	Foulkes (1986, 10606113); Friberg et al. (1974, 9282); Shaikh and Smith (1980, 2590); EPA (1986b, 199114); WHO (1972, 9739); WHO (1984, 10606114)[h]	–	–	B1[e,i]
CalEPA PHG {CalEPA, 2006a, 10615113}	0.0000063	EDOI	Ellis et al. (1979, 9281)[j]	–	–	–[k]
WHO GDWQ {WHO, 2011d, 10605331}	–[l]	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2012a, 2509015}	**0.0001**	**$UCDL_{10}$**	**Buchet et al. (1990, 81536); Järup et al. (2000, 55721); Suwazono et al. (2006, 187161)[m]**	–	–	–
HC GDWQ {HC, 2020b, 10586919}	–[n]	–	–	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; EDOI = estimated daily oral intake; $UCDL_{10}$ = 95% lower confidence limit on the urinary cadmium dose associated with a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily dose (ADD), minimal risk level (MRL), or reference dose (RfD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment did not derive an oral reference value but reports the provisional tolerable intake of 0.4–0.5 mg/week or 0.057–0.071 mg/day established by WHO (1972, 9739).

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The carcinogenicity assessment was last revised in 1987; the oral RfD was last revised in 1989 {U.S. EPA, 1989b, 10605332}.

[g] Oral RfD for cadmium in drinking water; a separate oral RfD for food was also derived (0.001 mg/kg/day).

[h] The NOAEL does not reflect information from any single study; rather, it is based on data obtained from many studies on the toxicity of cadmium in both humans and animals which show that a concentration of 200 µg cadmium/g in wet weight human renal cortex is the highest renal concentration not associated with significant proteinuria {U.S. EPA, 1986b, 199114}. The highest level of exposure associated with the lack of a critical effect (0.352 mg Cd/day, 0.005 mg/kg/day for a 70-kg adult) was modeled based on the NOAEL, assuming 4.5% absorption of the daily oral dose and 0.01% daily excretion of total body burden in a human by age 50 and an uncertainty factor of 10 {U.S. EPA, 1986b, 199114}.

[i] The health assessment states that there is sufficient evidence of carcinogenicity in rats and mice via the inhalation and intramuscular and subcutaneous injection routes of exposure; however, studies in rats and mice with oral administration have not shown evidence of carcinogenicity.

[j] The NOAEL does not reflect information from any single study; rather, it is based on toxicokinetic data obtained from several studies in humans which indicate that a urinary cadmium level of 1 µg/g creatinine (0.001 mg/g) would not result in increased excretion of biomarkers that are sensitive indicators of the onset of renal toxicity. Toxicokinetic data from several studies were used to estimate a daily intake (19 µg/day) that would maintain urinary cadmium levels below 1 µg/g creatinine. The daily intake was converted to an ADD (0.0063 µg/kg/day) by applying a total UF of 50.

[k] This health assessment did not derive a cancer descriptor based on EPA Guidelines for Carcinogen Risk Assessment, but reports that cadmium and cadmium compounds are listed on the California Proposition 65 List as "known to cause cancer" {CalEPA, 2006a, 10615113}. The health assessment states that there is sufficient evidence that cadmium is a human carcinogen, but there is insufficient information on carcinogenic potential from exposure via the oral route for quantitative risk assessment.

[l] This health assessment did not derive an oral reference value but reports the provisional tolerable monthly intake of 25 µg/kg body weight established by JECFA (2011, 10615288).

[m] The POD ($UCDL_{10}$) does not reflect information from any single study; a meta-analysis of available environmental exposure studies was conducted to estimate an internal dose corresponding to a 10% excess risk of low-molecular-weight proteinuria (urinary cadmium dose, UCD_{10}). The lowest UCD_{10} (1.34 µg/g creatinine) was estimated from the European database (including the critical studies listed) and the 95% lower confidence limit ($UCDL_{10}$) of 0.5 µg/g creatinine was selected as the POD.

[n] This health assessment did not derive an oral reference value but adopts a tolerable daily intake of 0.0008 mg/kg/day based on the tolerable monthly intake of 25 µg/kg established by JECFA (2011, 10615288).

The health assessment selected for SYR 4 is the ATSDR Toxicological Profile {ATSDR, 2012a, 2509015} (bolded in Table 6-20) because it was the most recent assessment to derive an oral chronic toxicity value and used new science to derive toxicity values. Although there was one more recent health assessment for cadmium, the HC GDWQ {HC, 2020b, 10586919}, this health assessment did not derive an oral reference value but adopts a tolerable daily intake of 0.0008 mg/kg/day based on the tolerable monthly intake of 25 µg/kg established by JECFA (2011, 10615288). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the ATSDR Toxicological Profile {ATSDR, 2012a, 2509015}, a chronic-duration oral MRL of 0.0001 mg/kg/day was derived. ATSDR conducted a meta-analysis of several environmental exposure dose-response studies to estimate the internal cadmium dose corresponding to a 10% excess risk of low molecular weight proteinuria. In its meta-analysis, ATSDR stratified studies and subsequent dose estimates by geographic location. The lowest internal cadmium dose was derived from the aggregation of European studies, consisting of seven critical studies {Buchet, 1990, 81536; Järup, 2000, 55721; Suwazono, 2006, 187161}. Pharmacokinetic models using data from these studies determined that a lifetime (to age 55) cadmium intake of 0.33 µg/kg/day in females would result in a urinary cadmium dose level ($UCDL_{10}$) corresponding to 0.5 µg cadmium/g creatinine. A total uncertainty factor (UF) of 3 was applied for intraspecies variability. After applying the total UF, the oral RfD for cadmium was calculated to be 0.1 µg/kg/day, or 0.0001 mg/kg/day {ATSDR, 2012a, 2509015}.

The ATSDR Toxicological Profile {ATSDR, 2012a, 2509015} does not assign a cancer descriptor for cadmium. Based on the weight of evidence (limited human and sufficient animal data), EPA categorized cadmium as B1 "probable human carcinogen" {U.S. EPA, 1989b, 10605332} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. However, this characterization describes the human carcinogenic potential of inhaled cadmium, because "There are no positive studies of orally ingested cadmium suitable for quantitation" {U.S. EPA, 1989b, 10605332}. This classification is based on limited evidence from occupational human studies, sufficient evidence of carcinogenicity in rodents following inhalation and intramuscular and subcutaneous injection, and evidence of

carcinogenicity when rodents received oral administration of cadmium salts {U.S. EPA, 1987h, 10606112; U.S. EPA, 1989b, 10605332}.

6.1.7.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the HC GDWQ was used to assign the date limit {HC, 2020b, 10586919}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for cadmium was defined as one year prior to July 2020, resulting in a search date range from July 1, 2019 to March 4, 2022. From this literature search, 7,058 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Four-hundred and seventy-six of these 7,058 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 6,582 of the 7,058 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-21.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for cadmium and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024U.S. EPA, 2024a, 11346388}).

Table 6-21. Evidence Stream Heat Map Results for Cadmium[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	2,145
Environmental Fate	–	3,198
Human	All	3,019
	Epidemiologic Quantitative Analyses	245
In Vitro	–	2,374
No Tag	–	241
Total Unique Studies		**6,582**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.7.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-22 shows the comparison of the basis for the existing and potential MCLGs for cadmium.

Table 6-22. Comparison of the Basis for the Existing and Potential MCLGs for Cadmium

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987h, 10606112)	–	–	–	D	–	–	–	–	–	–
EPA (1986b, 199114)	Friberg et al. (1974, 9282)	Kidney damage	–	–	0.0005	25%[e]	General Population	70 kg adult, 2 L/day	0.005	–
Relevant Health Assessment Identified in SYR 4										
EPA (1989b, 10605332)	–	–	–	[d]	–	–	–	–	–	–
ATSDR (2012a, 2509015)	Buchet et al. (1990, 81536); Järup et al. (2000, 55721); Suwazono et al. (2006, 187161)	10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10})	–	–	0.0001	25%[e]	General Population	33.8 mL/kg/day	–	0.0007[f]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] EPA designated cadmium B1, "probable human carcinogen," based on sufficient evidence of carcinogenicity in rats and mice via the inhalation and intramuscular and subcutaneous injection routes of exposure; however, studies in rats and mice with oral administration have not shown evidence of carcinogenicity.

[e] This departure from the default RSC of 20% was based on evidence of greater bioavailability of cadmium from water in comparison with food {U.S. EPA, 1989c, 18941}.

[f] Based on the revised "Group B1" cancer classification under the EPA 1986 Guidelines for Carcinogen Risk Assessment, the MCLG for cadmium could be potentially revised to zero; however, an updated assessment of cancer based on the current 2005 EPA Guidelines for Carcinogen Risk Assessment is needed {U.S. EPA, 2005d, 10263976}.

6.1.7.5 SYR 4 Health Effects Conclusion

The existing NPDWR for cadmium was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.0005 mg/kg/day {U.S. EPA, 1986b, 199114}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 25%, EPA set the MCLG at 0.005 mg/L and assigned cadmium a cancer classification of D, "not classifiable as to human carcinogenicity," according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the ATSDR Toxicological Profile {ATSDR, 2012a, 2509015} to derive the potential MCLG because it was a recent health assessment and used newer science to derive toxicity values. Based on an RfD of 0.0001 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 25% {U.S. EPA, 2016c, 6557097}, EPA calculated a potential MCLG of 0.007 mg/L. Based on the weight of evidence indicating limited human and sufficient animal data, the cancer classification for cadmium was updated to B1, "probable human carcinogen," based on the 1986 EPA Cancer Guidelines {U.S. EPA, 1986a, 199530}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.005 mg/L to the potential MCLG of 0.0007 mg/L.

6.1.8 Chlordane (CAS# 57-74-9 | DTXSID7020267)

6.1.8.1 Basis of the Existing MCLG

EPA published the current NPDWR for chlordane on January 30, 1991, establishing an MCLG of zero {U.S. EPA, 1991a, 5499}. The MCLG of zero is based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987i, 94968}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.002 mg/L based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.1.8.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for chlordane that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in 6-23.

Table 6-23. Assessments Identified for Chlordane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 1986c, 10509762}[d]	0.00005	LEL	Not Reported[e]	1.3	Not Reported[f]	B2[g]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987i, 94968}	0.00005	LOAEL	Ihui et al. (1983, 10534151)	1.3[h]	IRDC (1973, 62460); NCI (1977a, 62437)	B2[g]
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	0.00005	LOAEL	Ihui et al. (1983, 10534151)	1.3[h]	IRDC (1973, 62460); NCI (1977a, 62437)	B2[g]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG and Memo Update {CalEPA, 1997a, 10489802; 2006b, 10489849}	0.00001, 0.000033[i]	LOAEL	Cassidy et al. (1994, 47712)	1.3	NCI (1977a, 62437)	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1998, 2509044}	0.0005	NOAEL	Khasawinah and Grutsch (1989a, 67433); Velsicol Chemical Corporation (1983, 10573313)	**0.35[j]**	**IRDC (1973, 62460); NCI (1977a, 62437); Khasawinah and Grutsch (1989b, 67434)[k]**	**B2[g,l]**
WHO Guideline for Drinking-water Quality {WHO, 2004a, 10509440}	0.0005[m]	NOAEL	Hayakawa et al. (1983, 62455)[n]	–	–	–
ATSDR Toxicological Profile {ATSDR, 2018a, 1065240}	0.0006	NOAEL	Khasawinah and Grutsch (1989b, 67434)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LEL = lowest effect level; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The source of the information in this row is a 1986 memorandum from the Hazard Evaluation Division of EPA's Office of Pesticides and Toxic Substances that summarizes health assessments of chlordane completed by several branches including the Toxicology Branch and the Cancer Assessment Group. The memo does not report the references for the critical study used to derive the toxicity values.

[e] The oral reference value (a provisional ADI) was based on liver effects seen in male rats following ingestion of chlordane for 2.5 years. The health assessment did not provide any identifying information for the selected critical study beyond a brief description of the effects. Based on the description of effects that was provided, the critical study appears to be Ihui et al. (1983, 10534151).

[f] The EPA OPP HHRA did not provide any identifying information for the CSF critical study beyond a brief description of the results. Based on the description that was provided, the critical studies appear to be IRDC (1973, 62460) and NCI (1977a, 62437).

[g] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[h] The human cancer potency factor reported in these health assessments represents the geometric mean of the four potency estimates derived from four mouse data sets by fitting the linearized multistage model to each data set.

[i] CalEPA's PHG for chlordane was published in 1997 and updated with a memorandum in 2006. The memo summarized updated information for chlordane and concluded that the PHG should not be changed. The memo noted that the LOAEL reported in the 1997 PHG would have resulted in an ADD of 0.00001 mg/kg/day. The memo also reported a child-specific noncancer reference dose of 0.000033 mg/kg/day for chlordane, which was derived by the Integrated Risk Assessment Branch of CalEPA's Office of Environmental Health Hazard Assessment in 2005 {CalEPA, 2005a, 2773023}. Both values were derived using the same critical study and POD but the RfDs differed based on the uncertainty factors applied.

[j] The EPA IRIS Chemical Assessment Summary reports that the CSF is based on the geometric mean of the cancer potency estimates for five mouse data sets.

[k] Khasawinah and Grutsch (1989a, 67433) is also described in an earlier unpublished study {Velsicol Chemical Corporation, 1983, 10573313}, and the hepatocellular carcinoma incidence data from that unpublished report is used, in part, to derive the EPA IRIS CSF value.

[l] In addition to classifying chlordane as category B2, "probable human carcinogen," the EPA IRIS Chemical Assessment Summary for chlordane states that, "using the 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}, chlordane would be characterized as a likely carcinogen in humans."
[m] This provisional TDI (PTDI), reported in the WHO GDWQ for the development of the Guideline for Drinking-water Quality, was first derived as an ADI by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1986 {JMPR, 1987, 10534166} and was converted to a PTDI by JMPR in 1994 {JMPR, 1994, 6591479}.
[n] Although it is undetermined, Hayakawa et al. (1983, 62455) and Ihui et al. (1983, 10534151) may refer to the same study.

The health assessment selected for SYR 4 for chlordane is the 1998 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1997, 2509044} (bolded in Table 6-23) because it is the most recent EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. Additionally, no health assessments post-dating the 1998 EPA IRIS Chemical Assessment Summary consider new science. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The EPA IRIS Chemical Assessment Summary reported that three critical studies in mice {IRDC, 1973, 62460; NCI, 1977a, 62437; Khasawinah and Grutsch, 1989a, 67433} were considered when deriving the oral cancer slope factor (CSF) for chlordane. Although two of these studies {IRDC, 1973, 62460; NCI, 1977a, 62437} were limited by methodological problems, high dose levels, and excessive mortality, all three studies demonstrated adverse liver effects following chronic chlordane exposure. The IRDC study {IRDC, 1973, 62460} orally exposed groups of 100 male and 100 female CD-1 mice to chlordane at doses of 0, 5, 25, or 50 ppm for 18 months (equivalent to 0, 0.71, 3.57, and 7.14 mg/kg/day according to IRIS) {U.S. EPA, 1997, 2509044}. There was a significant increase in hepatic carcinomas in both male and female mice in the 3.57 and 7.14 mg/kg/day groups {U.S. EPA, 1997, 2509044}. The NCI study {NCI, 1977a, 62437} is a 2-year cancer bioassay of B6C3F1 mice (50 animals/sex/dose). Mice were orally exposed to chlordane via diet, and doses had to be adjusted during the study due to excessive toxicity {NCI, 1977a, 62437}. The time-weighted average doses for male mice were 29.9 and 56.2 ppm (approximately 4.3 and 8.0 mg/kg/day, respectively), and doses for female mice were 30.1 and 63.8 ppm (approximately 4.3 and 9.1 mg/kg/day, respectively). There was a significant dose-related trend for increased hepatocellular carcinoma in both sexes of mice. Note that rats were also included in this NCI bioassay, but the rats did not develop hepatocellular carcinomas at any dose; thus, the rat data were not used in IRIS's final CSF derivation. In Khasawinah and Grutsch (1989a, 67433), ICR mice (80 mice/sex/dose) were exposed to 0, 1, 5, or 12.5 ppm chlordane via diet (corresponding to 0, 0.15, 0.75, or 1.875 mg/kg/day, respectively) for 104 weeks. Hepatic necrosis and hepatic neoplasia were observed in the higher dose groups of male mice {Khasawinah and Grutsch, 1989a, 67433}. Male mice exposed to 12.5 ppm chlordane showed significantly increased incidence of hepatocellular adenomas {Khasawinah and Grutsch, 1989a, 67433}. Liver adenocarcinomas were also observed in dosed male mice {Khasawinah and Grutsch, 1989a, 67433}; these tumor incidence data are reported in an earlier report of the same study {Velsicol Chemical Corporation, 1983, 10573313} and were used in calculating the cancer slope factor {U.S. EPA, 1997, 2509044}.

The oral cancer slope factor was calculated to be 0.35 $(mg/kg/day)^{-1}$ based on mouse tumor data {U.S. EPA, 1997, 2509044}. Specifically, the geometric mean was calculated from five cancer slope factors using hepatocellular carcinoma incidence data from five mouse datasets (CD-1 males and females, B6C3F1 males and females, and ICR males) from the three critical studies cited in the IRIS Chemical Assessment Summary {U.S. EPA, 1997, 2509044}.

The EPA IRIS Chemical Assessment Summary noted that EPA classified chlordane as a "probable human carcinogen" (Group B2) {U.S. EPA, 1997, 2509044} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, based on the findings of liver carcinogenicity in mice in multiple studies. The 1998 EPA assessment also noted that under the 1996 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1996a, 83524}, chlordane would be

characterized as a "likely carcinogen in humans" by all routes of exposure {U.S. EPA, 1997, 2509044}. The current MCLG for chlordane {U.S. EPA, 1991a, 5499} established an MCLG of zero based on the B2 "probable human carcinogen," classification per the 1986 cancer guidelines {U.S. EPA, 1986a, 199530}. Therefore, the available noncancer toxicity values were not considered for potential MCLG derivation; the MCLG of zero based on the cancer classification is protective of the adverse noncancer effects.

6.1.8.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the 2018 ATSDR Toxicological Profile was used to assign the start date limit {ATSDR, 2018a, 1065240}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for chlordane was defined as one year prior to April 2017 resulting in search date range of April 1, 2016 to March 10, 2022.

From this literature search, 262 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Six of these 262 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 256 of the 262 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-24.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for chlordane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024U.S. EPA, 2024a, 11346388}).

Table 6-24. Evidence Stream Heat Map Results for Chlordane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	129
Environmental Fate	–	97
Human	All	149
	Epidemiologic Quantitative Analyses	13
In Vitro	–	87
No Tag	–	6
Total Unique Studies		**256**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.8.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-25 shows the comparison of the basis for the existing and potential MCLGs for chlordane.

Table 6-25. Comparison of the Basis for the Existing and Potential MCLGs for Chlordane

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987i, 94968)	IRDC (1973, 62460); NCI (1977a, 62437)	Hepatocellular carcinoma	1.3, Geometric Mean[d]	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (1997, 2509044)	IRDC (1973, 62460); NCI (1977a, 62437); Khasawinah and Grutsch (1989b, 67434)	Hepatocellular carcinoma	0.35, Geometric Mean[d]	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] CSF is based on the geometric mean of the cancer potency estimates for four mouse data sets.

6.1.8.5 SYR 4 Health Effects Conclusion

The existing NPDWR for chlordane was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987i, 94968} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero {U.S. EPA, 1991a, 5499}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1998 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1997, 2509044} to derive the potential MCLG because it is the most recent EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. Based on the analysis and conclusion presented in the selected health assessment, the cancer classification was maintained at B2, "probable human carcinogen," according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. For chlordane, more recent information does not support a change to the MCLG.

6.1.9 Monochlorobenzene (Chlorobenzene) (CAS# 108-90-7 | DTXSID4020298)

6.1.9.1 Basis of the Existing MCLG

EPA published the current NPDWR for monochlorobenzene on January 30, 1991, establishing both an MCLG and an MCL of 0.1 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.02 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1988d, 10520442} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.9.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for monochlorobenzene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-26.

Table 6-26. Assessments Identified for Monochlorobenzene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987j, 10509766}	0.043[d]	NOAEL	NTP (1985a, 10489888)	–	–	D[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988d, 10520442}	0.02[d]	NOAEL	Knapp et al. (1971, 1973232) Hazleton Laboratories (1967, 808660)[f]	–	–	D[e]
HC GDWQ {HC, 1988, 5099080}	0.0089[d]	NOAEL	Kluwe et al. (1985, 1946463)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989a, 6574259}[g]	**0.02[d]**	**NOAEL**	**Knapp et al. (1971, 1973232) Hazleton Laboratories (1967, 808660)[f]**	–	–	D[e]
ATSDR Toxicological Profile and Addendum {ATSDR, 1990, 625325; 2013, 10489752}[h]	0.4[i]	NOAEL	NTP (1985b, 201699)	–	–	–
WHO GDWQ {WHO, 2004b, 1239468}	0.0857	NOAEL	NTP (1985a, 10489888); Kluwe et al. (1985, 1946463)[j]	–	–	–
EPA ORD PPRTV {U.S. EPA, 2006b, 1257833}	Refer to IRIS	–	–	–	–	Refer to IRIS
CalEPA PHG {CalEPA, 2014, 10489858}	0.03[k]	$BMDL_{05}$	Nair et al. (1987, 1946437)	–	–	–
ATSDR Toxicological Profile {ATSDR, 2020; 7473279}	0.07[l]	$BMDL_{10}$	Hazleton Laboratories (1967, 808660)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{05}$ = 95% lower confidence limit on the benchmark dose for a 5% response; $BMDL_{10}$ = benchmark dose lower bound, where the change in response is likely to be smaller than 10%.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] An adjustment factor of 5/7× was applied to the oral reference value to account for discontinuous exposure (gavage dosing regimen was administered 5 days/week).

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] Knapp et al. (1971, 1973232) is an abstract that includes results from two studies conducted by Hazleton Laboratories on behalf of the Monsanto Company. The OW Drinking Water Criteria Document and IRIS Chemical Assessment Summary both cite the 13-week dog study described in this abstract and refer to the unpublished study report as Hazleton (1967) and Monsanto Co. (1967), respectively. In the references section for this document, the study is cited as Hazleton Laboratories (1967, 808660).

[g] Oral RfD last revised 1989; carcinogenicity assessment last revised 1990.

[h] The 2013 addendum to the Toxicological Profile provided updated scientific and regulatory data but did not change the MRL derived in the 1990 Toxicological Profile.

[i] Intermediate-duration oral MRL; a chronic MRL was not derived because human exposure data were lacking and the one animal toxicology study did not evaluate a sufficient number of endpoints and test animals.

[j] Kluwe et al. (1985, 1946463) describes the 2-year cancer bioassay study that is also reported in NTP (1985b, 201699).

[k] This ADD is based on data from a two-generation reproductive study in rats exposed to monochlorobenzene vapor; the $BMDL_{05}$ was converted from ppm in air to an equivalent dose in mg/kg/day{CalEPA, 2014, 10489858}.

[l] Intermediate-duration oral MRL; a chronic-duration oral MRL was not derived because the chronic oral database was insufficient.

The health assessment selected for SYR 4 for monochlorobenzene, or chlorobenzene, is the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989a, 6574259} (bolded in Table 6-26) because it is the most recent EPA health assessment that derives the most health protective oral toxicity value, and it used the best available science in its evaluation of non-cancer risk. Although more recent health assessments are available for monochlorobenzene, the CalEPA PHG {CalEPA, 2014, 10489858}, WHO GDWQ {WHO, 2004b, 1239468}, and the ATSDR Toxicological Profiles {ATSDR, 1990, 625325; 2013, 10489752}, are less health protective than the EPA IRIS health assessment. In addition, the EPA ORD PPRTV {U.S. EPA, 2006b, 1257833} health assessment refers to the EPA IRIS assessment. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 1989/1990 EPA health assessment selected the critical study for monochlorobenzene was a 13-week subchronic oral toxicity study in dogs, Knapp et al. (1971, 1973232), previously cited as an unpublished report {Hazleton Laboratories, 1967, 808660}. Male and female beagle dogs were given gelatin capsules of 0, 27.25, 54.5, or 272.5 mg/kg/day of monochlorobenzene 5 days/week for 13 weeks {Knapp et al., 1971, 1973232; Hazleton Laboratories, 1967, 808660}. Histopathologic changes in liver were observed at 54.5 mg/kg/day and greater, including slight bile duct proliferation, cytologic alterations, and leukocytic infiltration of the stroma. In addition to the liver changes, more severe effects were also observed (e.g., death, body weight loss, changes in hematology and clinical chemistry, and pathologic changes in kidney, liver, gastrointestinal mucosa, and hematopoietic tissue) at the highest dose of 272.5 mg/kg/day {Knapp et al., 1971, 1973232; Hazleton Laboratories, 1967, 808660}. Histopathologic changes in liver was selected as the critical effect {U.S. EPA, 2003f, 666927}. The initial NOAEL of 27.25 mg/kg/day was adjusted with a factor of 5/7× to account for discontinuous exposure because the gavage dosing regimen was administered for only 5 days out of each week, and the adjusted NOAEL was calculated to be 19 mg/kg/day and used as the POD. A total UF of 1,000 was applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, and 10 for extrapolation from subchronic to chronic exposure. After applying the total UF, the oral RfD was calculated to be 0.02 mg/kg/day.

The EPA IRIS Chemical Assessment Summary reported that EPA classified monochlorobenzene as "not classifiable as to human carcinogenicity" (Group D) due to a lack of human data and inadequate animal data {U.S. EPA, 1989a, 6574259} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.9.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for monochlorobenzene was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 1, 2022. From this literature search, 243 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty of these 243 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 223 of the 243 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-27.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for monochlorobenzene and specifically to inform EPA prioritization processes (see

Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-27. Evidence Stream Heat Map Results for Monochlorobenzene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	34
Environmental Fate	–	139
Human	All	52
	Epidemiologic Quantitative Analyses	2
In Vitro	–	56
No Tag	–	32
Total Unique Studies		**223**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.9.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-28 shows the comparison of the basis for the existing and potential MCLGs for monochlorobenzene.

Table 6-28. Comparison of the Basis for the Existing and Potential MCLGs for Monochlorobenzene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1988d, 10520442)	–	–	–	D	–	–	–	–	–	–
EPA (1988d, 10520442)	Knapp et al. (1971, 1973232) Hazleton Laboratories (1967, 808660)	Histopathological changes in the liver	–	–	0.02	20%	General Population	70 kg adult, 2 L/day	0.1	–
Relevant Assessment Identified in SYR 4										
EPA (1989a, 6574259)	–	–	–	D	–	–	–	–	–	–
EPA (1989a, 6574259)	Hazleton Laboratories (1967, 808660); Knapp et al. (1971, 1973232)	Histopathological changes in liver	–	–	0.02	20%	General Population	33.8 mL/ kg/day	–	0.1

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.9.5 SYR 4 Health Effects Conclusion

The existing NPDWR for monochlorobenzene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.02 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.1 mg/L and assigned monochlorobenzene a cancer classification of D, "not classifiable as to human carcinogenicity"{U.S. EPA, 1988d, 10520442; U.S. EPA, 1991a, 5499}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989a, 6574259} to derive the potential MCLG because it is the most recent EPA health assessment that derived the most health protective oral toxicity value and used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.02 mg/kg/day {U.S. EPA, 1989a, 6574259}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.1 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 0.1 mg/L.

6.1.10 Cyanide (CAS# 57-12-5 | DTXSID6023991)

6.1.10.1 Basis of the Existing MCLG

EPA published the current NPDWR for cyanide on July 17, 1992, establishing both an MCLG and an MCL of 0.2 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.02 mg/kg/day {U.S. EPA, 1992i, 677130} and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992i, 677130}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). During the first Six-Year Review cycle (SYR 1), EPA recommended a revision to the best available technologies (BATs) for cyanide to clarify that "chlorine" should be "alkaline chlorine" to avoid potential for the formation of harmful cyanogen chloride {U.S. EPA, 2003g, 1261321}. EPA promulgated that revision in EPA's *National Primary Drinking Water Regulations: Minor Corrections and Clarification to Drinking Water Regulations; National Primary Drinking Water Regulations for Lead and Copper* {U.S. EPA, 2004c, 10492447}.

6.1.10.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for cyanide that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-29.

Table 6-29. Assessments Identified for Cyanide

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987k, 10510377}	0.022	NOAEL	Howard and Hanzal (1955, 64704)	–	–	D[d]
HC GDWQ {HC, 1991, 10524698}[e]	–	–	–	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992i, 677130}	0.02	NOAEL	Howard and Hanzal (1955, 64704)	–	–	D[d]
CalEPA PHG {CalEPA, 1997b, 10489804}	0.02[f]	NOAEL	Howard and Hanzal (1955, 64704)	–	–	–
ATSDR Toxicological Profile {ATSDR, 2006b, 669233}	0.05[g]	NOAEL	NTP (1993, 5915912)	–	–	–
WHO GDWQ {WHO, 2009b, 10509456}	0.045[h]	NOAEL	NTP (1993, 5915912)	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2010c, 723657}	**0.0006[i]**	**$BMDL_{10}$**	**NTP (1993, 5915912)**	–	–	I[j]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] HC did not derive an acceptable daily intake (ADI) for cyanide but set a maximum allowable concentration of 0.2 mg/L for free cyanide in drinking water.

[f] This RfV was calculated by EPA using the POD (NOAEL of 10.8 mg/kg/day) and total UF of 500 identified by CalEPA and rounded to one significant figure.

[g] This is an intermediate-duration MRL. A chronic-duration MRL was not derived for cyanide because of the lack of suitable data in humans and animals {ATSDR, 2006b, 669233}.

[h] This TDI is intended for short-term use. WHO (2009b, 10509456) stated that development of a guideline for long-term exposure to cyanide was not considered necessary.

[i] This is an oral RfD for free cyanide. The EPA IRIS Toxicological Review {U.S. EPA, 2010c, 723657} notes that "the ability of the individual cyanogenic species to dissociate and release free cyanide in aqueous solution (and at physiological pHs) should be taken into consideration."

[j] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2010 EPA IRIS Toxicological Review {U.S. EPA, 2010c, 723657} (bolded in Table 6-29) because it was the most recent EPA health assessment and used the best available science to derive a toxicity value (i.e., BMD modeling). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals. In this 2010 EPA IRIS health assessment, EPA chose an NTP study {NTP, 1993, 5915912} as the critical study to derive a POD for cyanide. In this subchronic study, F344N rats and B6C3F1 mice (10/sex/exposure concentration/species) were administered sodium cyanide in drinking water at concentrations of 0, 3, 10, 30, 100, or 300 ppm for 13 weeks. Significant dose-dependent effects on male reproductive endpoints were observed in both rats and mice, including decreased cauda and whole epididymis weights, decreased testes weight, and altered sperm parameters. The decrease in cauda epididymis weight in male rats was selected as the critical effect

because it was the most sensitive endpoint indicative of male reproductive toxicity. EPA used BMD modeling to determine a benchmark dose lower limit ($BMDL_{10}$) of 1.9 mg/kg/day for this critical effect, which was used as the POD. A total uncertainty factor of 3,000 was then applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, 10 for extrapolation from subchronic to chronic exposure, and 3 for database deficiencies due to the lack of information regarding potential multigenerational reproductive effects and the lack of a sensitive neurodevelopmental study. After applying the total UF, the oral RfD was calculated to be 6×10^{-4} mg/kg/day.

As reported in the 2010 EPA IRIS Toxicological Review, EPA concluded that there is "inadequate information to assess the carcinogenic potential" of cyanide {U.S. EPA, 2010c, 723657} according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976} due to the lack of adequate carcinogenicity studies in animals or humans.

6.1.10.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for cyanide was defined as one year prior to December 2015, resulting in search date range from December 1, 2014 to January 25, 2022.

From this literature search, 2,420 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two-hundred and three of these 2,420 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 2,217 of the 2,420 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-30.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for cyanide and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-30. Evidence Stream Heat Map Results for Cyanide[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	819
Environmental Fate	–	529
Human	All	1,052
	Epidemiologic Quantitative Analyses	26
In Vitro	–	960
No Tag	–	215
Total Unique Studies		**2,217**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.10.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-31 shows the comparison of the basis for the existing and potential MCLGs for cyanide.

Table 6-31. Comparison of the Basis for the Existing and Potential MCLGs for Cyanide

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992i, 677130)	–	–	–	D	–	–	–	–	–	–
EPA (1992i, 677130)	Howard and Hanzal (1955, 64704)	Absence of clinical and histologic effects	–	–	0.02	20%	General Population	70 kg adult, 2 L/day	0.2	–
Relevant Health Assessment Identified in SYR 4										
EPA (2010c, 723657)	–	–	–	I	–	–	–	–	–	–
EPA (2010c, 723657)	NTP (1993, 5915912)	Decreased cauda epididymis weight in rats	–	–	0.0006	20%	General Population	33.8 mL/kg/day	–	0.004

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.10.5 SYR 4 Health Effects Conclusion

The existing NPDWR for cyanide was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}, and it established an MCLG of 0.2 mg/L for cyanide based on an RfD of 0.02 mg/kg/day {U.S. EPA, 1992i, 677130} and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992i, 677130}. Using the RfD of 0.02 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA derived the MCLG of 0.2 mg/L. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2010 EPA IRIS Toxicological Review {U.S. EPA, 2010c, 723657} to derive the potential MCLG because it was the most recent EPA health assessment and used the best available science to derive a toxicity value. EPA calculated a potential MCLG of 0.004 mg/L based on an RfD of 0.0006 mg/kg/day {U.S. EPA, 2010c, 723657}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%. In the 2010 EPA IRIS Toxicological Review, the cancer classification for cyanide was updated to I, "inadequate information to assess carcinogenic potential," in accordance with EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.2 mg/L to the potential MCLG of 0.004 mg/L.

6.1.11 Dalapon (CAS# 75-99-0 | DTXSID2021575)

6.1.11.1 Basis of the Existing MCLG

EPA published the current NPDWR for dalapon on July 17, 1992, establishing both an MCLG and an MCL of 0.2 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.03 mg/kg/day {U.S. EPA, 1992e, 10492395}. EPA did not provide a cancer classification for dalapon at the time of promulgation {U.S. EPA, 1992g, 10587719}.

6.1.11.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for dalapon that were published prior to the cut-off date of November 2020, from the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-32.

Table 6-32. Assessments Identified for Dalapon

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1988g, 10532678}	0.03[d]	NOAEL	Paynter et al. (1960, 6579689)	–	–	–
EPA OW Health Advisory {U.S. EPA, 1989d, 10532766}	0.03[d]	NOAEL	Paynter et al. (1960, 6579689)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992e, 10492395}	**0.027[d]**	**NOAEL**	**Paynter et al. (1960, 6579689)**	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The commercial-grade dalapon sodium used in the study by Paynter et al. (1960, 6579689) contained 65% of the pure sodium salt of dalapon, which yielded a NOAEL of 15 mg/kg/day. To calculate the NOAEL for pure dalapon acid (used to derive the RfD), 15 mg/kg/day was multiplied by the ratio of molecular weight of dalapon and its sodium salt (143/165) and the purity of sodium dalapon (0.65), yielding a NOAEL of 8 mg/kg/day for pure dalapon acid.

The health assessment selected for SYR 4 is the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992, 10492395} (bolded in Table 6-32) because it was the most recent EPA health assessment available for dalapon and used the best available science in its evaluation of noncancer risk. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The EPA OW Drinking Water Criteria Document {U.S. EPA, 1992e, 10492395} chose a two-year toxicity study {Paynter, 1960, 6579689} as the critical study to derive a chronic oral RfD. In this study, albino rats (24/sex/group) were fed diets containing 0, 5, 15, or 50 mg commercial dalapon sodium salt/kg bw/day (mg/kg/day) for two years. A significant increase in kidney-to-body weight ratios of male adult rats receiving 50 mg/kg/day was observed compared with controls. This outcome was selected as the critical effect for selecting a POD for RfD derivation. Since the commercial grade dalapon sodium salt used in the study had a purity of only 65%, the dose was adjusted by multiplying the NOAEL dose by the ratio of the molecular weight of dalapon (143) to its sodium salt (165). Thus, the reported NOAEL of 15 mg/kg/day was converted to 8.45 mg/kg/day, which is the POD used to derive the RfD. A total uncertainty factor (UF) of 300 was applied: 10 for interspecies variability, 10 for intraspecies variability, and 3 for database deficiencies due to incomplete data on chronic toxicity. After applying the total UF, the oral RfD was calculated to be 0.027 mg/kg/day.

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S EPA, 1986a, 199530}, dalapon is classified as Group D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992e, 10492395}. Dalapon did not undergo a complete evaluation and determination of human carcinogenic potential as part of the 1988 EPA IRIS assessment {U.S. EPA, 1988g, 10532678}.

6.1.11.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for dalapon was defined as one year prior to December 2015 resulting in a search date range from December 1, 2014 to February 22, 2022.

From this literature search, 482 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Thirty of these 482 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 452 of the 482 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-33.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for dalapon and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-33. Evidence Stream Heat Map Results for Dalapon[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	165
Environmental Fate	–	76
Human	All	258
	Epidemiologic Quantitative Analyses	3
In Vitro	–	214
No Tag	–	50
Total Unique Studies		**452**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.11.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-34 shows the comparison of the basis for the existing and potential MCLGs for dalapon.

Table 6-34. Comparison of Existing and Potential MCLGs for Dalapon

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1989d, 10532766)	–	–	–	–	–	–	–	–	–	–
EPA (1992e, 10492395)	Paynter et al. (1960, 6579689)	Increased kidney weight	–	–	0.027	20%	General Population	70 kg adult, 2 L/day	0.2	–
Relevant Health Assessment Identified in SYR 4										
EPA (1989d, 10532766)	–	–	–	D	–	–	–	–	–	–
EPA (1992e, 10492395)	Paynter et al. (1960, 6579689)	Increased kidney-to-body weight ratio	–	–	0.027	20%	General Population	33.8 mL/kg/day	–	0.2

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.11.5 SYR 4 Health Effects Conclusion

The existing NPDWR for dalapon was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.027 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.2 mg/L {U.S. EPA, 1992g, 10587719}. EPA did not provide a cancer classification for dalapon at the time of promulgation {U.S. EPA, 1992, 10587719}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA OW Drinking Water Criteria Document {U.S. EPA, 1992e, 10492395} to derive the potential MCLG because it was the most recent EPA health assessment available for dalapon and used the best available science in its evaluation of noncancer risk. Based on an RfD of 0.027 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.2 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 0.2 mg/L.

6.1.12 1,2-Dibromo-3-chloropropane (DBCP) (CAS# 96-12-8 | DTXSID3020413)

6.1.12.1 Basis of the Existing MCLG

EPA published the current NPDWR for DBCP on January 30, 1991 {U.S. EPA, 1991a, 5499}, which established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen," for DBCP {U.S. EPA, 1988e, 10709984} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.0002 mg/L, based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.1.12.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for DBCP that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-35.

Table 6-35. Assessments Identified for 1,2-Dibromo-3-chloropropane (DBCP)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	–	–	–	1.4[d]	Wilbur et al. (1985, 597184)	B2[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988e, 10709984}	–	–	–	1.4[d]	Wilbur et al. (1985, 597184)	B2[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991f, 3350457}	–	–	–	–	–	–
WHO GDWQ {WHO, 2003d, 10634791}	–	–	–	–	–	–
EPA ORD PPRTV {U.S. EPA, 2006a, 1258143}	0.0002	NOAEL[f]	Foote et al. (1986a, 63488; 1986b, 63487)	**0.8[g]**	**Hazleton Laboratories (1977a, 10534510)**	**L[h]**
ATSDR Toxicological Profile {ATSDR, 2018b, 5932454}	0.002[i]	LOAEL	Foote et al. (1986a, 63488; 1986b, 63487)	–	–	–
CalEPA PHG {CalEPA, 2020, 10534721}	0.000044	NOAEL	Rao et al. (1982, 63533)	1	Hazleton Laboratories (1977a, 10534510)	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral RfV are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), population-adjusted dose (PAD), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] CSF are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment does not derive a CSF but rather reports the value determined by the Carcinogen Assessment Group {Wilbur et al., 1985, 597184} based on data from a Hazleton Laboratories study in rats {Hazleton Laboratories, 1977a, 10534510}.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] This EPA ORD PPRTV {U.S. EPA, 2006, 1258143} indicates that all of the available chronic LOAELs are higher than the 1.3 mg/kg/day subchronic LOAEL from the critical study (Foote et al., 1986a, 63488; Foot et al., 1986b, 63487), and that the NOAEL (0.7 mg/kg/day) is the most appropriate basis for derivation of a chronic RfD.

[g] EPA concluded that DBCP is carcinogenic by a mutagenic mode of action. The CSF does not reflect presumed early-life susceptibility and therefore, ADAFs should be applied to this slope factor when assessing cancer risks (U.S. EPA, 2005b, 88823).

[h] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[i] This is an intermediate-duration oral MRL. A chronic oral MRL was not derived due to insufficient data.

The health assessment selected for SYR 4 is the 2006 EPA Provisional Peer Reviewed Toxicity Values for 1,2-Dibromo-3-Chloropropane {U.S. EPA, 2006a, 1258143} because it is the most recent EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for DBCP (bolded in Table 6-35). Although more recent health assessments were available, including an ATSDR Toxicological Profile {ATSDR, 2018b, 5932454} and CalEPA PHG document {CalEPA, 2020, 10534721}, they did not introduce new science (i.e., the toxicity values in these health assessments were not based on new critical studies) compared to the 2006 EPA Provisional Peer Reviewed Toxicity Values for 1,2-Dibromo-3-Chloropropane {U.S. EPA, 2006a, 1258143}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2006 EPA PPRTV health assessment derived a cancer slope factor of 0.8 $(mg/kg/day)^{-1}$ based on the critical study of Hazleton Laboratories (1977a, 10534510). In this study, adult Charles River rats

(60/sex/treatment) were exposed to DBCP at dose levels of 0, 0.3, 1.0, or 3.0 mg/kg/day in the diet for 104 weeks, with estimated dosage intakes of 0, 0.24, 0.80, and 2.39 mg/kg/day. Increased incidences of stomach and kidney tumors were observed in both sexes and hepatocellular carcinomas were observed in adult male rats. EPA calculated a benchmark dose lower confidence limit on a 10% response ($BMDL_{10}$) of 0.46 mg/kg/day based on the combined incidence of renal tubular cell adenomas and carcinomas in adult male rats, and this value was used as the POD. From this POD, EPA derived a human oral cancer slope factor of 0.8 per mg/kg/day, which represents $0.1/BMDL_{10}$(human) from extrapolating the rat value ($0.1/BMDL_{10}$) multiplied by $(WH/WR)^{1/4}$, where WH = 70 kg (human reference body weight) and WR = 0.38 kg (adult male rat body weight) based on EPA rat reference body weights {U.S. EPA, 1988f, 10264083}.

EPA concluded that DBCP is carcinogenic by a mutagenic MOA and described DBCP as "likely to be carcinogenic to humans" {U.S. EPA, 2006a, 1258143}, which corresponds to a cancer descriptor of L based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. Because DBCP is classified as "likely to be carcinogenic to humans," based on the 2005 current cancer guidelines, the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.12.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the 2020 CalEPA PHG was used to assign the date limit {CalEPA, 2020, 10534721}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for DBCP was defined as one year prior to December 2017, resulting in a search date range from December 1, 2016 to March 7, 2022.

From this literature search, 14 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 14 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 13 of the 14 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-36.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for DBCP and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-36. Evidence Stream Heat Map Results for 1,2-Dibromo-3-chloropropane (DBCP)[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	0
Environmental Fate	–	4
Human	All	6
	Epidemiologic Quantitative Analyses	2
In Vitro	–	2
No Tag	–	3
Total Unique Studies		**13**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.12.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-37 shows the comparison of the basis for the existing and potential MCLGs for DBCP.

Table 6-37. Comparison of the Basis for the Existing and Potential MCLGs for 1,2-Dibromo-3-chloropropane (DBCP)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1988e, 10709984)	Hazleton Laboratories (1977a, 10534510)	Liver, kidney, and stomach tumors	1.4	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2006a, 1258143}	Hazleton Laboratories (1977a, 10534510)	Renal tubular cell adenomas, carcinomas in male rats	0.8	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.12.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,2-dibromo-3-chloropropane (DBCP) was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1988e, 10709984} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA ORD PPRTV {U.S. EPA, 2006a, 1258143} to derive the potential MCLG because it is the most recent EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for DBCP. The EPA ORD PPRTV derived a CSF of 0.8 $(mg/kg/day)^{-1}$ and an updated cancer descriptor of L, "likely to be carcinogenic to humans," for DBCP according to EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For DBCP, more recent information does not support a change to the MCLG.

6.1.13 1,1-Dichloroethylene (CAS# 75-35-4 | DTXSID8021438)

6.1.13.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,1-dichloroethylene on July 8, 1987. The NPDWR established both an MCLG and an MCL of 0.007 mg/L {U.S. EPA, 1987m, 3809376}. EPA based the MCLG on a reference dose of 0.01 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1987n, 10509765} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. See Table 3-1 for more information on cancer classification. A risk management safety factor of 10 was applied in the calculation of the MCLG to account for possible carcinogenicity {U.S. EPA, 1987m, 3809376} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.1.13.2 Results of the SYR 4 Health Assessment Search

The following table shows final health assessments relevant to chronic toxicity available for 1,1-dichloroethylene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-38.

Table 6-38. Assessments Identified for 1,1-Dichloroethylene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987n, 10509765}	0.01	LOAEL	Quast et al. (1983, 64323)	–	–	C[d]
ATSDR Toxicological Profile {ATSDR, 1994, 11347323}	0.009	LOAEL	Quast et al. (1983, 64323)	–	–	–
HC GDWQ {HC, 1994, 10529370}	0.003	LOAEL	Quast et al. (1983, 64323)	–	–	–
CalEPA PHG {CalEPA, 1999a, 10489835}	0.003[e]	LOAEL	Quast et al. (1983, 64323)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary; EPA IRIS Toxicological Review {U.S. EPA, 2002f, 1739804}[f]	**0.05**	**$BMDL_{10}$**	**Quast et al. (1983, 64323)**	**–**	**–**	**–[g]**
WHO GDWQ {WHO, 2005a, 10509453}	–[h,i]	–	–	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}

[e] POD/UF calculated based on a POD of 9 mg/kg/day and a UF of 3,000.

[f] The IRIS Chemical Assessment Summary indicates that EPA conducted a comprehensive review of toxicological studies published through May 2005 and that no new health effects data were identified that would be directly useful in the revision of the existing RfD or the carcinogenicity assessment for 1,1-dichloroethylene.

[g] The 2002 IRIS Toxicological Review notes that data are inadequate for an assessment of human carcinogenic potential by the oral route and provide suggestive evidence of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents based on EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}.

[h] The WHO GDWQ notes that International Programme on Chemical Safety (IPCS) developed a TDI for 1,1-dichloroethylene based on the critical effect of hepatocellular mid-zonal fatty change in female rats reported in the study by Quast et al. (1983, 64323). A $BMDL_{10}$ of 4.6 mg/kg/day was determined. An uncertainty factor of 100 (for inter- and intraspecies variation) was applied to the $BMDL_{10}$, resulting in a TDI of 0.046 mg/kg bw {WHO, 2003e, 10509425}.

[i] WHO (2005a, 10509453) states that a potential health-based value of 0.14 mg/L for 1,1-dichloroethylene "is significantly higher than the concentrations of [1,1-dichloroethylene] that are normally found in drinking-water. It is therefore considered unnecessary to set a formal guideline value for [1,1-dichloroethylene] in drinking-water."

The health assessment selected for SYR 4 is the 2002 EPA IRIS Toxicological Review {U.S. EPA, 2002f, 1739804} (bolded in Table 6-38) because this is an EPA health assessment that derives an oral toxicity value and used the best available science to evaluate non-cancer risks. Although a more recent health assessment by WHO {WHO, 2005a, 10509453} was available, it did not derive a relevant toxicity value. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2002 EPA IRIS Toxicological Review identified Quast et al. (1983, 64323) as the critical study to identify a POD for 1,1-dichloroethylene RfD derivation. In this study, adult Sprague-Dawley rats (80 rats/sex for controls and 48 rats/sex/dose for treated groups) were exposed to 1,1-dichloroethylene in drinking water at concentrations of 0, 50, 100, or 200 ppm daily for two years {Quast et al., 1983, 64323}. Female rats showed an increased incidence of minimal hepatocellular fatty changes at 100 and 200 ppm and this critical effect was selected as the basis for the POD. EPA used BMD modeling to derive a benchmark dose lower limit on a 10% response ($BMDL_{10}$) of 4.6 mg/kg/day for hepatocellular fatty changes in female rats. A total uncertainty factor (UF) of 100 was applied: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF, the oral RfD was calculated to be 0.05 mg/kg/day.

The 2002 EPA IRIS Toxicological Review noted that, based on the 1999 EPA draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}, the data are "inadequate for assessment of carcinogenic potential by the oral route based on the absence of statistically or biologically significant tumors in limited bioassays in rats and mice balanced against the suggestive evidence in male mice in a single bioassay by inhalation and the limited evidence of genotoxicity" {U.S. EPA, 2002f, 1739804}.

6.1.13.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,1-dichloroethylene was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to February 24, 2022. From this literature search, 81 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 81 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3 for further information).

From this literature search, 81 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 81 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 80 of the 81 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-39.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,1-dichloroethylene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-39. Evidence Stream Heat Map Results for 1,1-Dichloroethylene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	18
Environmental Fate	–	23
Human	All	47
	Epidemiologic Quantitative Analyses	2
In Vitro	–	28
No Tag	–	5
Total Unique Studies		**80**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.13.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-40 shows the comparison of the basis for the existing and potential MCLGs for 1,1-dichloroethylene.

Table 6-40. Comparison of the Basis for the Existing and Potential MCLGs for 1,1-Dichloroethylene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987n, 10509765)	–	–	–	C	–	–	–	–	–	–
EPA (1987n, 10509765)	Quast et al. (1983, 64323)	Liver toxicity, fatty change	–	–	0.01	20%	General Population	70 kg/adult, 2 L/day	0.007[d]	
Relevant Health Assessment Identified in SYR 4										
EPA (2002f, 1739804)	–	–	–	–[e]	–	–	–	–	–	–
EPA (2002f, 1739804)	Quast et al. (1983, 64323)	Liver toxicity, fatty change	–	–	0.05	20%	General Population	33.8 mL/ kg/day	–	0.3

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity.

[e] The 2002 IRIS Toxicological Review notes that data are inadequate for an assessment of human carcinogenic potential by the oral route and provide suggestive evidence of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents based on EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}.

6.1.13.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,1-dichloroethylene was published on July 8, 1987 {U.S. EPA, 1987m, 3809376}. Based on an RfD of 0.01 mg/kg/day {U.S. EPA, 1987n, 10509765}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg) {U.S. EPA, 2019, 7267482}, and an RSC of 20%, EPA set the MCLG at 0.007 mg/L and assigned 1,1-dichloroethylene a cancer descriptor of C, "possible human carcinogen" {U.S. EPA, 1987n, 10509765} according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. An additional risk management safety factor of 10 was applied to the MCLG to account for possible carcinogenicity. See Table 3-1 for more information on cancer classification and application of a risk management safety factor.

Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2002 EPA IRIS Toxicological Review {U.S. EPA, 2002f, 1739804} to derive the potential MCLG because this EPA health assessment derives an oral toxicity value and uses the best available science to evaluate non-cancer risks. Based on an RfD of 0.05 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.3 mg/L. In the 2002 EPA IRIS Toxicological Review, EPA determined a cancer descriptor of C, "possible human carcinogen," for 1,1-dichloroethylene based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The Toxicological Review also noted that, data are inadequate for an assessment of human carcinogenic potential by the oral route and provide suggestive evidence of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents according to EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}. As a result of this conclusion the risk management safety factor of 10 was removed when calculating the potential MCLG in SYR 3. Similarly, SYR 4 removed the risk management safety factor of 10 when calculating the potential MCLG. EPA concluded that new health effects information supports raising the current MCLG of 0.007 mg/L to the potential MCLG of 0.3 mg/L.

6.1.14 cis-1,2-Dichloroethylene (CAS# 156-59-2 | DTXSID2024030)

6.1.14.1 Basis of the Existing MCLG

EPA published the current NPDWR for cis-1,2-dichloroethylene on January 30, 1991, establishing both an MCLG and an MCL of 0.07 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.01 mg/kg/day {U.S. EPA, 1990c, 1739793}and a cancer classification of D, "not classifiable as to human carcinogenicity" { U.S. EPA, 1990c, 1739793}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.14.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for cis-1,2-dichloroethylene that were published prior to the cut-off date of November 2020, that were identified prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-41.

Table 6-41. Assessments Identified for cis-1,2-Dichloroethylene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990c 1739793}	0.01	NOAEL	McCauley et al. (1990, 7415498)[d]	–	–	D[e]
EPA OW Health Advisory {U.S. EPA, 1990d, 10492393}	0.01	NOAEL	McCauley et al. (1990, 7415498)[d]	–	–	D[e]
ATSDR Toxicological Profile {ATSDR, 1996, 723873}	0.3[f]	NOAEL	McCauley et al. (1990, 7415498)[d]	–	–	–
WHO GDWQ {WHO, 2003f, 6305381}	0.017[g]	NOAEL	Barnes et al. (1985, 200220)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010b, 10493648}	**0.002**	**$BMDL_{10}$**	**McCauley et al. (1995, 5237; 1990, 7415498)[d]**	–	–	I[h]
EPA ORD PPRTV {U.S. EPA, 2011e, 1258158}	Refer to IRIS[i]	–	–	–	–	Refer to IRIS[i]
CalEPA PHG {CalEPA, 2018a, 10489860}	0.00125[j]	$BMDL_{1SD}$	McCauley et al. (1995, 5237; 1990, 7415498)[d]	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{1SD}$ = benchmark dose level associated with 1 standard deviation from the control mean; $BMDL_{10}$ = the 95% lower confidence limit on the benchmark dose (BMD_{10}) corresponding to a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily dose (ADD), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The critical study was a subchronic 90-day oral study {McCauley et al., 1990, 7415498} [unpublished report], later published as McCauley et al., 1995, 5237}.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] Intermediate-duration oral MRL; a chronic oral MRL was not derived because no human or animal data were located regarding health effects after chronic oral exposure to 1,2-dichloroethylene.

[g] The TDI reported was developed jointly for the trans and cis isomers {WHO, 2003f, 6305381}. The TDI value are based on a NOAEL for the trans isomer {Barnes et al., 1985, 200220}.

[h] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[i] This health assessment defers to EPA IRIS Chemical Assessment Summary for cis-1,2-dichloroethylene {U.S. EPA, 2010b, 10493648}.

[j] POD/UF calculated based on a $BMDL_{1SD}$ of 3.76 mg/kg/day and a total UF of 3,000.

The health assessment selected for SYR 4 is the 2010 EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010b, 10493648} (bolded in Table 6-41) because it is an EPA assessment that derives an oral toxicity value, used the best available science in its evaluation of non-cancer risk, and designated an updated cancer classification based on the current, 2005 EPA Cancer Guidelines (2005d, 10263976). Although more recent health assessments were available {CalEPA, 2018a, 10489860; U.S. EPA, 2011e, 1258158}, they did not introduce any new science (e.g., they used the same critical study as the 2010 EPA IRIS Chemical Assessment Summary). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The critical study used in the 2010 EPA IRIS Chemical Assessment Summary to derive the cis-1,2-dichloroethylene RfD is McCauley et al. (1995, 5237), which was previously an unpublished report {McCauley, 1990, 7415498}. In this sub-chronic oral study, Sprague-Dawley rats (10/sex/dose) were dosed for 90 days with cis-1,2-dichloroethylene in corn oil by oral gavage at doses of 0, 0.33, 1.00, 3.00, or 9.00 mmol/kg/day {McCauley, 1995, 5237}. EPA reported that these dose levels correspond to 0, 32, 97, 291, or 872 mg/kg/day, respectively. Significant increases in liver weight were observed in both sexes at ≥ 97 mg/kg/day, and significant increases in kidney weight in male rats were observed at all dose levels {McCauley, 1995, 5237}. EPA considered both effects as candidate critical effects. BMD modeling was subsequently used to estimate the $BMDL_{10}$ for relative liver and kidney weights in male rats. Of these two endpoints, relative kidney weight yielded the lowest $BMDL_{10}$ and was selected as the more sensitive endpoint and critical effect for the POD. Thus, the $BMDL_{10}$ of 5.1 mg/kg/day for relative kidney weight in male rats was selected as the POD for cis-1,2-dichloroethylene. A total uncertainty factor of 3,000 was then applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, 10 for extrapolation from sub-chronic to chronic exposure, and 3 for database deficiencies due to the lack of reproductive and developmental toxicity data. After applying the total UF, the oral RfD was calculated to be 0.002 mg/kg/day.

Following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA concluded that there is "inadequate information to assess the carcinogenic potential" of cis-1,2-dichloroethylene and classified it as Group I based on the absence of epidemiological studies in humans and lack of animal studies designed to evaluate its carcinogenic potential {U.S. EPA, 2010b, 10493648}.

6.1.14.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the CalEPA PHG was used to assign the date limit {CalEPA, 2018a, 10489860}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for cis-1,2-dichloroethylene was defined as one year prior to July 2018, resulting in a search date range from July 1, 2017 to March 23, 2022.

From this literature search, 72 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 72 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3for further information). Following SWIFT-Review, 71 of the 72 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-42.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for cis-1,2-dichloroethylene and specifically to inform EPA prioritization processes (see

Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-42. Evidence Stream Heat Map Results for cis-1,2-Dichloroethylene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	0
Environmental Fate	–	70
Human	All	8
	Epidemiologic Quantitative Analyses	0
In Vitro	–	15
No Tag	–	0
Total Unique Studies		**71**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.14.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-43 shows the comparison of the basis for the existing and potential MCLGs for cis-1,2-dichloroethylene.

Table 6-43. Comparison of the Basis for the Existing and Potential MCLGs for cis-1,2-Dichloroethylene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990c, 1739793)	–	–	–	D	–	–	–	–	–	–
EPA (1990c, 1739793)	McCauley et al. (1990, 7415498)	Decreases in hematocrit	–	–	0.01	20%	General Population	70 kg adult, 2 L/day	0.07	–
Relevant Health Assessment Identified in SYR 4										
EPA (2010b, 10493648)	–	–	–	I	–	–	–	–	–	–
EPA (2010b, 10493648)	McCauley et al. (1995, 5237; 1990, 7415498)	Increased relative kidney weight in males	–	–	0.002	20%	General Population	33.8 mL/ kg/day	–	0.01

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.14.5 SYR 4 Health Effects Conclusion

The existing NPDWR for cis-1,2-dichloroethylene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.01 mg/kg/day {U.S. EPA, 1990c, 1739793}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.07 mg/L and assigned cis-1,2-dichlorotheylene a cancer classification of D, "not classifiable as to human carcinogenicity," according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010b, 10493648} to derive the potential MCLG because it is an EPA assessment that derives an oral toxicity value, used the best available science in its evaluation of non-cancer risk, and designated an updated cancer descriptor. Based on an RfD of 0.002 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.01 mg/L. The EPA IRIS Chemical Assessment Summary noted that, based on the analysis and conclusion presented in this health assessment, the cancer classification for cis-1,2-dichloroethylene was updated to I, "inadequate information to assess carcinogenic potential," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.07 mg/L to the potential MCLG of 0.01 mg/L.

6.1.15 Di(2-ethylhexyl)adipate (DEHA) (CAS# 103-23-1 | DTXSID0020606)

6.1.15.1 Basis of the Existing MCLG

EPA published the current NPDWR for di(2-ethylhexyl)adipate (DEHA) on July 17, 1992 {U.S. EPA, 1992g, 10587719}. The NPDWR established both an MCLG and an MCL of 0.4 mg/L. EPA based the MCLG on a reference dose of 0.6 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992j, 2310207}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. A risk management safety factor of 10 was applied in the calculation of the MCLG to account for possible carcinogenicity (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.1.15.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for di(2-ethylhexyl)adipate that were published prior to the cut-off date of November 2020, for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-44.

Table 6-44. Assessments Identified for Di(2-ethylhexyl)adipate

Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1992b, 6574222}[d]	**0.6**	**NOAEL**	**ICI Central Toxicology Laboratory (1988, 6781636); Tinston (1988, 6580309)**	0.0012	NTP (1982a, 2310121)	C[e]

Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992j, 2310207}	0.6	NOAEL	ICI (1988, 6781636); Tinston (1988, 6580309)	0.0012	NTP (1982a, 2310121)	Refer to IRIS[f]
CalEPA PHG {CalEPA, 2003c, 10489845}	0.028[g]	NOAEL	ICI (1988, 6781636); Tinston (1988, 6580309)	–	–	–
WHO GDWQ {WHO, 2004c, 10509441}	0.28	NOAEL	ICI (1988, 6781636)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] In the 1992 EPA IRIS Chemical Assessment Summary, the carcinogenicity assessment was last revised in 1991 and the oral RfD was last revised in 1992.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] This health assessment cites the cancer classification from the 1992 EPA IRIS Chemical Assessment Summary.

[g] EPA calculated this POD/UF using the POD of 28 mg/kg/day identified by CalEPA and the total UF of 1,000.

The health assessment selected for SYR 4 is the 1992 EPA IRIS Chemical Assessment Summary for di(2-ethylhexyl)adipate (bolded in Table 6-44) because it is an EPA assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk {U.S. EPA, 1992b, 6574222}. Although more recent health assessments were available, including the EPA OW Drinking Water Criteria Document {U.S. EPA, 1992j, 2310207}, California EPA PHG {CalEPA, 2003c, 10489845}, and WHO GDWQ {WHO, 2004c, 10509441}, these assessments used the same critical study {ICI, 1998, 6781636; Tinston, 1998, 6580309} as the 1992 EPA IRIS Chemical Assessment Summary. Furthermore, the more recent health assessments did not use updated methodologies (e.g., BMD modeling for POD derivation) to derive toxicity values. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the 1992 EPA IRIS Chemical Assessment Summary, EPA selected two unpublished critical studies {ICI, 1988, 6781636; Tinston, 1988, 6580309} to derive an oral RfD. In a rat teratogenicity feeding study {ICI, 1988, 6781636}, di(2-ethylhexyl)adipate (DEHA) was administered to Wistar-derived pregnant rats (24 rats/dose) at dose levels of 0, 300, 1,800, or 12,000 ppm in the diet from gestational day (GD) 1 to GD 22, and effects in developing fetuses were assessed. In an accompanying one-generation rat reproductive study {Tinston, 1988, 6580309}, the effects on fertility, other reproductive outcomes, and gross and histological parameters were examined in Wistar-derived rats of both sexes (15 males/dose and 30 females/dose) exposed to DEHA in the diet at the same dose levels (0, 300, 1,800, or 12,000 ppm) for 10 weeks until mating. Dosing of dams via the diet continued post-partum for approximately 18–19 weeks of total exposure. From these two studies, a NOAEL of 1800 ppm or 170 mg/kg/day was determined from several endpoints (i.e., changes in body weight and liver weight in parental animals, reduced ossification and dilated ureters in fetuses, reduced offspring weight gain, total litter weight, and litter size) and this was used as the POD. A total uncertainty factor of 300 was then applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, and 3 for database deficiencies due to the lack of multi-generation reproductive data and lack of non-rodent data. After applying the total UF, the oral RfD for DEHA was calculated to be 0.6 mg/kg/day.

Following the EPA 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA determined that di(2-ethylhexyl)adipate is a class C "possible human carcinogen" based on an increased incidence of liver tumors seen in female mice, the structural relationship of DEHA to other similarly classified nongenotoxic compounds, and the absence of human data {U.S. EPA, 1992b, 6574222}.

6.1.15.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for di(2-ethylhexyl)adipate was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to February 25, 2022. From the literature searches performed, a total of 54 unique studies were identified following review of the literature. Following SWIFT-Review, 50 of the 54 unique studies were tagged to the evidence stream categories shown in 6-45.

From this literature search, 54 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Four of these 54 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 50 of the 54 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-45.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for di(2-ethylhexyl)adipate and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-45. Evidence Stream Heat Map Results for Di(2-ethylhexyl)adipate (DEHA)[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	9
Environmental Fate	–	16
Human	All	32
	Epidemiologic Quantitative Analyses	1
In Vitro	–	11
No Tag	–	4
Total Unique Studies		**50**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.15.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-46 shows the comparison of the basis for the existing and potential MCLGs for di(2-ethylhexyl)adipate.

Table 6-46. Comparison of the Basis for the Existing and Potential MCLGs for Di(2-ethylhexyl)adipate

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992j, 2310207)	NTP (1982a, 2310121)	Combined hepatocellular adenomas and carcinomas	0.0012	C	–	–	–	–	–	–
EPA (1992j, 2310207)	ICI (1988, 6781636); Tinston (1988, 6580309)	Changes in body weight and liver weight, increased liver weight of male and female parents, reduced ossification and slightly dilated ureters in fetuses, and reduced offspring weight gain, total litter weight, and litter size	–	–	0.6	20%	General Population	70 kg adult, 2 L/day	0.4[d]	–
Relevant Health Assessment Identified in SYR 4										
EPA (1992b, 6574222)	NTP (1982a, 2310121)	Combined hepatocellular adenomas and carcinomas	0.0012	C	–	–	–	–	–	–
EPA (1992b, 6574222)	ICI (1988, 6781636); Tinston (1988, 6580309)	Changes in body weight and liver weight, increased liver weight of male and female parents, reduced ossification and slightly dilated ureters in fetuses, and reduced offspring weight gain, total litter weight, and litter size	–	–	0.6	20%	Women of childbearing age	35.4 mL/kg/day	–	0.3[d,e]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90^{th} percentile drinking water intake (mL/kg/day).

[d] This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity.

[e] The potential MCLG is based on the same reference value and relative source contribution as the existing MCLG, but relies on a different exposure factor. The difference in values between the existing and potential MCLGs is due only to this use of different exposure factors {U.S. EPA, 2019, 7267482}.

6.1.15.5 SYR 4 Health Effects Conclusion

The existing NPDWR for di(2-ethylhexyl)adipate was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. The MCLG was based on an RfD of 0.6 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992b, 6574222}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Based on an RfD of 0.6 mg/kg/day {U.S. EPA, 1992b, 6574222}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), an RSC of 20%, and an additional risk management safety factor of 10 to account for possible carcinogenicity, an MCLG of 0.4 mg/L was derived. EPA assigned di(2-ethylhexyl)adipate a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992b, 6574222}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor). EPA followed the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2 to select the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1992b, 6574222} because it is an EPA assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer effects. In SYR 4, di(2-ethylhexyl)adipate maintained the cancer classification of C "possible human carcinogen," and therefore maintained application of the risk management safety factor of 10 to account for possible carcinogenicity. Based on an RfD of 0.6 mg/kg/day, an adjusted DWI-BW ratio of 35.4 mL/kg/day for women of childbearing age (13 to < 50 years) (see Section 4.2 for further information on target population selection), and an RSC of 20%, plus application of the risk management safety factor, EPA calculated a potential MCLG of 0.3 mg/L. EPA concluded that while the available health effects information alone do not support a change to the MCLG, there is a potential to lower the existing MCLG from 0.4 mg/L to the potential MCLG of 0.3 mg/L based on use of the updated exposure factor of 35.4 mL/kg/day for women of childbearing age.

6.1.16 Dinoseb (CAS# 88-85-7 | DTXSID3020207)

6.1.16.1 Basis of the Existing MCLG

EPA published the current NPDWR for dinoseb on July 17, 1992, establishing both an MCLG and an MCL of 0.007 mg/L {U.S. EPA, 1992g, 10587719} based on a reference dose of 0.001 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992c, 1003105}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.16.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for dinoseb that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-47.

Table 6-47. Assessments Identified for Dinoseb

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study[c]	Oral Cancer Slope Factor[d]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1988h, 10532507}	0.001	LOAEL	Hazleton Laboratories (1977, 1003102)	–	–	D[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study[c]	Oral Cancer Slope Factor[d]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989e, 10280593}	0.001	LOAEL	Dow Chemical (1981a, 1003079)	–	–	D[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992c, 1003105}	**0.001[f]**	**LOAEL**	**Hazleton Laboratories (1977, 1003102); Dow Chemical (1981b, 1003090; (1981a, 1003079)**	–	–	D[e]
EPA ORD PPRTV {U.S. EPA, 2002g, 1258200}	–	–	–	–[g]	–	–
CalEPA PHG {CalEPA, 2010d, 10489856}[h]	–	–	–	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), reference dose (RfD), or tolerable daily intake (TDI).

[c] The references for unpublished studies conducted for Dow Chemical Company by Hazleton Laboratories are referred to in multiple ways across health assessments. Dow Chemical (1981b, 1003090) is a 2-year feeding study and cancer bioassay in mice conducted by Hazleton Laboratories for Dow Chemical Company. Dow Chemical (1981a, 1003079) is a dietary three-generation rat reproduction study conducted by Hazleton Laboratories for Dow Chemical Company. Hazleton Laboratories (1977, 1003102) is a 2-year dietary study in rats conducted by Hazleton Laboratories for Dow Chemical Company.

[d] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The EPA OW Drinking Water Criteria Document derived an RfD based on a LOAEL of 1 mg/kg/day based on the following effects reported in the following three different studies: (1) decreased mean thyroid weights in all dosed male rats {Hazleton Laboratories, 1977, 1003102}; (2) decreased cystic endometrial hyperplasia and atrophy, hypospermatogenesis, and degeneration of the testes in mice {Dow Chemical, 1981b, 1003090}; and (3) decreased pup body weights at all dose levels in a 3-generation reproductive study in rats {Dow Chemical, 1981a, 1003079}.

[g] The EPA ORD PPRTV document reports that it was not feasible to derive an oral slope factor for dinoseb due to a lack of human data and inadequate animal data.

[h] This 2010 CalEPA memorandum reaffirms the PHG for dinoseb that was originally derived in 1997, but the 2010 memorandum does not report the RfD and the 1997 PHG document could not be located.

The health assessment selected for SYR 4 is the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992c, 1003105} (bolded in Table 6-47) because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Although more current health assessments were available for dinoseb, including the 2002 EPA ORD PPRTV {U.S. EPA, 2002g, 1258200} and the 2010 CalEPA PHG {CalEPA, 2010d, 10489856}, these health assessments did not report relevant toxicity values that could be used to derive a potential MCLG. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the OW Drinking Water Criteria Document {U.S. EPA, 1992c, 1003105}, EPA selected three critical studies as the basis for deriving the RfD. The study by Hazleton Laboratories (1977, 1003102) identified a LOAEL of 1 mg/kg/day based on a decrease in mean thyroid weights in all dosed adult male rats. In this

study, tissues from a limited number of animals were examined histopathologically. A second study {Dow Chemical, 1981b, 1003090} completed a more comprehensive histopathological examination of tissues from mice fed diets containing 1, 3 or 10 mg/kg/day dinoseb for 100 weeks and also reported a LOAEL of 1 mg/kg/day, based on cystic endometrial hyperplasia and atrophy, hypospermatogenesis, and degeneration of the testes. This LOAEL was further supported by the results of a three-generation reproductive study {Dow Chemical, 1981a, 1003079}, in which 25 male and 25 female rats were administered dinoseb in the diet at doses of 0, 1, 3, or 10 mg/kg/day for 29 weeks (2 littering groups/generation). Decreased fetal weights and decreased pup body weights were observed at all dose levels. Because this developmental effect of decreased offspring weight was observed at all doses of dinoseb, a LOAEL of 1 mg/kg/day was determined. A total uncertainty factor (UF) of 1,000 was applied: 10 for interspecies variability, 10 for intraspecies variability, and 10 for extrapolation of the POD from the LOAEL. After applying the total UF, the oral RfD was calculated to be 0.001 mg/kg/day {U.S. EPA, 1992c, 1003105}.

The EPA OW Drinking Water Criteria Document classified dinoseb as Group D, "not classifiable as to human carcinogenicity," due to inadequate human and animal evidence {U.S. EPA, 1992c, 1003105} based on the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.16.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for dinoseb was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 7, 2022. From this literature search, 202 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Seven of these 202 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 195 of the 202 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-48.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for dinoseb and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-48. Evidence Stream Heat Map Results for Dinoseb[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	25
Environmental Fate	–	70
Human	All	151
	Epidemiologic Quantitative Analyses	1
In Vitro	–	32
No Tag	–	5
Total Unique Studies		**195**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.16.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-49 shows the comparison of the basis for the existing and potential MCLGs for dinoseb.

Table 6-49. Comparison of Existing and Potential MCLGs for Dinoseb

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992c, 1003105)	–	–	–	D	–	–	–	–	–	–
EPA (1992c, 1003105)	Hazleton Laboratories (1977, 1003102); Dow Chemical (1981b, 1003090; 1981a, 1003079)	Decreased thyroid weight (Hazleton Laboratories, 1977, 1003102); cystic endometrial hyperplasia and atrophy, hypospermatogenesis and degeneration of the testes (Dow Chemical, 1981b, 1003090); decreased fetal and pup body weight (Dow Chemical, 1981a, 1003079)	–	–	0.001	20%	General Population	70 kg adult, 2 L/day	0.007	–
Relevant Health Assessment Identified in SYR 4										
EPA (1992c, 1003105)	–	–	–	D	–	–	–	–	–	–

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
EPA (1992c, 1003105)	Hazleton Laboratories (1977, 1003102); Dow Chemical (1981b, 1003090; 1981a, 1003079)	Decreased thyroid weight (Hazleton Laboratories, 1977, 1003102); cystic endometrial hyperplasia and atrophy, hypospermatogenesis and degeneration of the testes (Dow Chemical, 1981b, 1003090); decreased fetal and pup body weight (Dow Chemical, 1981a, 1003079)	–	–	0.001	20%	Women of childbearing age	35.4 mL/ kg/day	–	0.004[d]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] Difference from original MCLG based only on use of updated drinking water intake values (Table 3-63. Two-Day Average Consumer-Only Drinking Water Intake: Pregnant and Lactating Women, and Women of Child-Bearing Age [13 to < 50 years]) {U.S. EPA, 2019, 7267482}.

6.1.16.5 SYR 4 Health Effects Conclusion

The existing NPDWR for dinoseb was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.001 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.007 mg/L and assigned dinoseb a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992c, 1003105}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA followed the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2. EPA selected the EPA OW Drinking Water Criteria Document {U.S. EPA, 1992c, 1003105} used to support the NPDWR at rule promulgation {U.S. EPA, 1992g, 10587719} because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.001 mg/kg/day, an adjusted DWI-BW ratio of 35.4 mL/kg/day for women of childbearing age (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.004 mg/L. The exposure factor for women of childbearing age was selected because one of the critical effects is decreased fetal body weight, which resulted from gestational exposure. EPA concluded that the available health effects information does not support a change to the MCLG; however, there is a potential to lower the existing MCLG from 0.007 mg/L to the potential MCLG of 0.004 mg/L based on the updated exposure factor of 35.4 mL/kg/day.

6.1.17 Dioxin (2,3,7,8-TCDD) (CAS# 1746-01-6 | DTXSID2021315)

6.1.17.1 Basis of the Existing MCLG

EPA published the current NPDWR for dioxin on July 17, 1992 {U.S. EPA, 1992g, 10587719}, establishing an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1988c, 2192594} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 3×10^{-8} mg/L, based on analytical feasibility {U.S. EPA, 1992g, 10587719}.

6.1.17.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for dioxin that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-50.

Table 6-50. Assessments Identified for Dioxin (2,3,7,8-TCDD)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987o, 10535728}	1×10^{-9}	LOAEL	Schantz et al. (1979, 787868); Murray et al. (1979, 197983)	1.56×10^{5}	Kociba et al. (1978, 1818)	B2[d]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988c, 2192594}	1×10^{-9}	LOAEL	Schantz et al. (1979, 787868); Murray et al. (1979, 197983)	1.56×10^{5}	Kociba et al. (1978, 1818)	**B2[d]**

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile {ATSDR, 1998, 197033}	1×10^{-9}	LOAEL	Schantz et al. (1992, 50032)	–[e]	–	–
CalEPA PHG {CalEPA, 2010b, 10489855}[f]	4.69×10^{-10}	LOAEL	NTP (2004, 197605)	**7.7×10^{5}**	**NTP (2004, 197605)**	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2012c, 10494330}[g]	7×10^{-10}	LOAEL	Mocarelli et al. (2008, 199595)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessments and chronic toxicity values bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] The ATSDR Toxicological Profile cites the CSF of 1.56×10^{5} $(mg/kg/day)^{-1}$ reported in the EPA OW Health Advisory {U.S. EPA, 1987o, 10535728} and Drinking Water Criteria Document {U.S. EPA, 1988c, 2192594}.

[f] The oral reference value is the POD/UF.

[g] A cancer weight-of-evidence assessment was underway as of 2012 when the IRIS Chemical Assessment Summary for TCDD was last updated. However, the quantitative estimate of carcinogenic risk from oral exposure was not assessed.

The health assessments selected for SYR 4 are the 2010 CalEPA PHG {CalEPA, 2010b, 10489855} and the 1988 EPA OW Drinking Water Criteria Document for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) {U.S. EPA, 1988c, 2192594}. The 2010 CalEPA PHG was selected because it derived a CSF based on a more recent critical study {NTP, 2004, 197605} and used the best available science in its evaluation of cancer risk. EPA selected the 1988 Drinking Water Criteria Document for dioxin because it provides a cancer classification for dioxin, which serves as the basis for the MCLG of zero. Although the more recent EPA IRIS Chemical Assessment Summary {U.S. EPA, 2012c, 10494330} was available, it did not derive an oral cancer slope factor or designate a cancer descriptor. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2010 CalEPA health assessment derived a multi-site oral cancer potency factor of 7.7×10^{5} $(mg/kg/day)^{-1}$ based on increased incidence of multiple tumor types in the lung, liver, oral mucosa, pancreas, and uterus of female Sprague-Dawley rats following chronic oral gavage exposure to dioxin in an NTP study (2004, 197605), which was selected as the critical study. Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, dioxin is classified as Group B2, "probable human carcinogen," with sufficient animal data demonstrating carcinogenicity, but inadequate data in humans {U.S. EPA, 1988c, 2192594}. Because dioxin is classified as a "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.17.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for dioxin was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 8, 2022.

From this literature search, 2,864 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Eighty-two of these 2,864 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3for further information). Following SWIFT-Review, 2,782 of the 2,864 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-51.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for dioxin and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-51. Evidence Stream Heat Map Results for Dioxin[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,387
Environmental Fate	–	920
Human	All	1,600
	Epidemiologic Quantitative Analyses	114
In Vitro	–	1,140
No Tag	–	87
Total Unique Studies		**2,782**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.17.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-52 shows the comparison of the basis for the existing and potential MCLGs for dioxin (2,3,7,8-TCDD).

Table 6-52. Comparison of the Basis for the Existing and Potential MCLGs for Dioxin (2,3,7,8-TCDD)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1988c, 2192594)	Kociba et al. (1978, 1818)	Multiple tumor types and locations	1.56×10^5	B2	–	–	0	–
Relevant Health Assessments Identified in SYR 4								
CalEPA (2010b, 10489855)	NTP (2004, 197605)	Multiple tumor types and locations	7.7×10^5	–	–	–	–	–
EPA (1988c, 2192594)	–	–	–	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.17.5 SYR 4 Health Effects Conclusion

The existing NPDWR for dioxin was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1988c, 2192594} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG for dioxin at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the CalEPA PHG {CalEPA, 2010b, 10489855} because it derived a CSF based on a more recent critical study {NTP, 2004, 197605} and used the best available science in its evaluation of cancer risk for dioxin. EPA based the cancer classification on the EPA Drinking Water Criteria Document {U.S. EPA, 1988c, 2192594}, which serves as the basis for the MCLG of zero. Based on the analyses and conclusions presented in these health assessments, the cancer classification was maintained at B2. For dioxin, more recent information does not support a change to the MCLG.

6.1.18 Endrin (CAS# 72-20-8 | DTXSID6020561)

6.1.18.1 Basis of the Existing MCLG

EPA published the current NPDWR for endrin on July 17, 1992, establishing both an MCLG and an MCL of 0.002 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.0003 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992f, 10492397}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.18.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for endrin that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-53.

Table 6-53. Assessments Identified for Endrin

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	0.000045	NOAEL	Treon and Cleveland, (1955, 2315751)	–	–	E[d]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1989f, 10282542}[e]	0.0003	NOEL	Kettering Laboratory (1969, 1311675)[f]	–	–	D[d]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992f, 10492397}	**0.0003**	**NOAEL**	**CBI study cited in EPA (1987p, 10532311)[f]**	–	–	D[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA ORD PPRTV {U.S. EPA, 2002h, 1260311}	–	–	–	–[g]	–	Refer to IRIS
WHO GDWQ {WHO, 2004d, 10509442}	0.0002[h]	NOAEL	Not Reported[f]	–	–	–[i]
CalEPA PHG {CalEPA, 2016b, 10489859}	0.000022	$BMDL_{05}$	Jolley et al. (1969, 1311675)[f]	–	–	–[i]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; dash (–) = not provided; $BMDL_{05}$ = benchmark dose at the 95% lower confidence limit on a 5% response; CBI = confidential business information.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a, 199530).

[e] Oral RfD last revised 1988; carcinogenicity assessment last revised 1989.

[f] Based upon the study descriptions and the effects reported at the LOAEL, EPA assumed that the CBI study cited in EPA (1987p, 10532311), Jolley et al. (1969, 1311675), Kettering Laboratory (1969, 1311675) and the uncited critical study used by WHO (2004d, 10509442) all report on the same study.

[g] The EPA ORD PPRTV assessment concluded that a provisional oral slope factor for endrin could not be derived because there were no adequate human or animal oral cancer data demonstrating carcinogenic activity.

[h] The WHO GDWQ reports a provisional tolerable daily intake (PTDI) for endrin that was first derived as an ADI by FAO/WHO (1971, 10536246) and then converted to a PTDI by JMPR (1995, 6591479).

[i] This health assessment does not designate a cancer descriptor based on EPA's 1986 Guidelines for Carcinogen Risk Assessment but reports that there was inadequate evidence to assess the potential carcinogenicity of endrin for humans.

The health assessment selected for SYR 4 is the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992f, 10492397} (bolded in Table 6-53) because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Although more recent health assessments were available, including a CalEPA PHG {CalEPA, 2016b, 10489859} and a WHO GDWQ {WHO, 2004d, 10509442}, these assessments did not introduce new science (i.e., the toxicity value was based on the same or older critical study than the selected assessment). A more recent EPA ORD PPRTV {U.S. EPA, 2002h, 1260311} was also available; however, it did not report a relevant toxicity value for deriving a potential MCLG. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The critical study used in the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992f, 10492397} to derive the endrin RfD is a CBI study cited in EPA (1987p, 10532311). This 1969 chronic oral study in dogs is an unpublished report referenced by other health assessments on endrin under different study author names (i.e., Jolley et al. (1969, 1311675); Kettering Laboratory (1969, 1311675)). Beagle dogs (3–7/sex/dose) were exposed to 0, 0.1, 0.5, 1.0, 2.0, or 4.0 ppm endrin for two years via the diet. A LOAEL of 2.0 ppm and NOAEL of 1.0 ppm were identified based on mild histological lesions in liver (slight vacuolization of hepatic cells), increased relative liver weights, and occasional convulsions {U.S. EPA, 1992f, 10492397}. EPA converted the reported NOAEL of 1.0 ppm to 0.025 mg/kg/day {U.S. EPA, 1992f, 10492397}. Using the NOAEL of 0.025 mg/kg/day as the POD, a total uncertainty factor (UF) of 100 was applied: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF, the oral RfD was calculated to be 0.0003 mg/kg/day.

The 1992 EPA health assessment concluded that the database for carcinogenic effects of endrin was inadequate and the data were equivocal and thus classified endrin as Group D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992f, 10492397} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.18.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the 2016 CalEPA PHG document was used to assign the date limit {CalEPA, 2016b, 10489859}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for endrin was defined as one year prior to September 2016 resulting in a search date range from September 1, 2015 to March 8, 2022. From this literature search, 147 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Three of these 147 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 144 of the 147 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-54.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for dinoseb and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-54. Evidence Stream Heat Map Results for Endrin[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	57
Environmental Fate	–	83
Human	All	86
	Epidemiologic Quantitative Analyses	6
In Vitro	–	22
No Tag	–	5
Total Unique Studies		**144**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.18.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-55 shows the comparison of the basis for the existing and potential MCLGs for endrin.

Table 6-55. Comparison of the Basis for the Existing and Potential MCLGs for Endrin

Reference	Critical Study	Critical Effect	Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992f, 10492397)	–	–	–	D	–	–	–	–	–	–
EPA (1992f, 10492397)	CBI study cited in EPA (1987p, 10532311)	Mild histopathologic changes in liver, occasional convulsions	–	–	0.0003	20%	General Population	70 kg adult, 2 L/day	0.002	–
Relevant Health Assessment Identified in SYR 4										
EPA (1992f, 10492397)	–	–	–	D	–	–	–	–	–	–
EPA (1992f, 10492397)	CBI study cited in EPA (1987p, 10532311)	Mild histopathologic changes in liver, occasional convulsions	–	–	0.0003	20%	General Population	33.8 mL/kg/ day	–	0.002

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.18.5 SYR 4 Health Effects Conclusion

The existing NPDWR for endrin was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.0003 mg/kg/day {U.S. EPA, 1992f, 10492397}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.002 mg/L and assigned endrin a cancer classification of D {U.S. EPA, 1992f, 10492397}, "not classifiable as to human carcinogenicity," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA OW Drinking Water Criteria Document {U.S. EPA, 1992f, 10492397} to derive the potential MCLG because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.0003 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.002 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 0.002 mg/L.

6.1.19 Epichlorohydrin (CAS# 106-89-8 | DTXSID1020566)

6.1.19.1 Basis of the Existing MCLG

EPA published the current NPDWR for epichlorohydrin on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987q, 18929}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established a treatment technique requirement that limits the allowable level of epichlorohydrin monomer in the polymer that is added to water as a flocculent to remove particulates. Each water system is required to certify, in writing, to the state (using third-party or manufacturer's certification) that the combination (or product) of dose and monomer level does not exceed the following level: 0.01 percent residual epichlorohydrin monomer in polymer products used during water treatment and dosed at 20 mg/L (ppm) {U.S. EPA, 1991a, 5499}.

6.1.19.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for epichlorohydrin that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-56.

Table 6-56. Assessments Identified for Epichlorohydrin

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987q, 18929}	0.00216	LOAEL[d]	Laskin et al. (1980, 94977)	0.0099[e]	Konishi et al. (1980, 18712); Kawabata (1981, 18708)	B2[f]
EPA OW Health Advisory {U.S. EPA, 1987r, 10532283}	0.00216	LOAEL[d]	Laskin et al. (1980, 94977)	0.0099	Konishi et al. (1980, 18712)	B2[f]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1988d, 10532430}	–[g]	–	–	**0.0099**	**Konishi et al. (1980, 18712)**	**B2[f]**
WHO GDWQ {WHO, 2004e, 10509443}	0.00014	LOAEL	Wester et al. (1985, 18652)	–	–	–
EPA ORD PPRTV {U.S. EPA, 2006c, 1260313}	0.006	LOAEL	Toth et al. (1991, 65058)	Refer to IRIS	Refer to IRIS	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The LOAEL from Laskin et al. (1980, 94977) was based on a LOAEL from an inhalation exposure study that was then converted to an oral exposure value using the following exposure factors: amount of air breathed by a rat; a 6 hour/day, 5 day/week exposure period; an inhalation absorption factor; and rat body weight.

[e] The Drinking Water Criteria Document cites the EPA Health Assessment Document for Epichlorohydrin {U.S. EPA, 1984b, 17614} for this value.

[f] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[g] The EPA IRIS Chemical Assessment Summary states that the oral RfD for epichlorohydrin "has been withdrawn pending further review by the RfD/RfC Work Group."

The health assessment selected for SYR 4 is the 1988 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988d, 10532430} (bolded in Table 6-56), because this is an EPA assessment that used the best available and most recent science in its evaluation of cancer risk and derivation of a cancer slope factor for epichlorohydrin. Although more recent health assessments are available, including the WHO GDWQ {WHO, 2004e, 10509443} and the EPA ORD PPRTV {U.S. EPA, 2006c, 1260313}, they did not use updated methodologies or they referred to the 1988 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988d, 10532430}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the 1988 EPA IRIS Chemical Assessment Summary, EPA selected the chronic drinking water exposure study by Konishi et al. (1980, 18712) as the critical study. In this study, male Wistar rats (18/dose) were exposed to 0, 375, 750, or 1500 ppm epichlorohydrin in drinking water for 81 weeks. Exposure was stopped intermittently between weeks 60–81 due to poor health of treated animals and decreased survival rates in all dose groups. The study reported increased incidences of forestomach hyperplasia and papillomas and squamous cell carcinomas in high-dose males. The forestomach tumors finding was selected as the critical effect and used to derive the CSF using a linearized multistage procedure accounting for extra cancer risk. Equivalent human doses were calculated assuming average adult body weight of 70 kg and water consumption of 2 L/day. The human cancer slope factor was subsequently derived as 0.0099 $(mg/kg/day)^{-1}$.

The 1988 EPA IRIS Chemical Assessment Summary reported that epichlorohydrin is a "probable human carcinogen" {U.S. EPA, 1988d, 10532430} according to EPA's 1986 Guidelines for Carcinogen Risk

Assessment {U.S. EPA, 1986a, 199530}. Human carcinogenicity data are inadequate but multiple rodent studies reported tumors following administration of epichlorohydrin by various exposure routes. Because epichlorohydrin is classified as a "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.19.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA ORD PPRTV {U.S. EPA, 2006c, 1260313} was used to assign the date limit. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for epichlorohydrin was defined as one year prior to October 2002, resulting in a search date range from October 1, 2001 to September 8, 2022.

From this literature search, 484 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Forty-seven of these 484 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 437 of the 484 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-57.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for epichlorohydrin and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-57. Evidence Stream Heat Map Results for Epichlorohydrin[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	108
Environmental Fate	–	143
Human	All	135
	Epidemiologic Quantitative Analyses	5
In Vitro	–	142
No Tag	–	105
Total Unique Studies		**437**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.19.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-58 shows the comparison of the basis for the existing and potential MCLGs for epichlorohydrin.

Table 6-58. Comparison of the Basis for the Existing and Potential MCLGs for Epichlorohydrin

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987q, 18929)	Konishi et al. (1980, 18712) and Kawabata (1981, 18708)	Papillomas and carcinomas of the forestomach of rats	0.0099	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (1988d, 10532430)	Konishi et al. (1980, 18712)	Papillomas and carcinomas of the forestomach of rats	0.0099	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.19.5 SYR 4 Health Effects Conclusion

The existing NPDWR for epichlorohydrin was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987q, 18929}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1988 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988d, 10532430} to derive the potential MCLG because this is an EPA assessment that used the best available and most recent science in its evaluation of cancer risk and its derivation of a cancer slope factor for epichlorohydrin. Based on the analysis and conclusion presented in this health assessment, the cancer classification was maintained at B2. For epichlorohydrin, more recent information does not support a change to the MCLG.

6.1.20 Fluoride (CAS# 16984-48-8 | DTXSID9049617)

6.1.20.1 Basis of the Existing MCLG

EPA published the current NPDWR for fluoride on April 2, 1986 {U.S. EPA, 1986d, 10634795}. The NPDWR established both an MCLG and an MCL of 4 mg/L to protect against crippling skeletal fluorosis {U.S. EPA, 1986d, 10634795}.The MCLG was derived from an estimated 20 mg/day chronic fluoride intake {U.S. EPA, 1985f, 6580525}, a human dose level at which adverse health effects of fluoride were not likely to occur {Shapiro, 1983, 11264440; Koop, 1984, 11264447; WHO, 1984, 10606114}. Though an RfD was not derived for fluoride, EPA determined that "the incidence of objectionable dental fluorosis (moderate and severe) does not generally impact a significant percentage of the population until the drinking water concentration approaches 2.0 mg F/L" {U.S. EPA, 1985f, 6580525}. Further, EPA determined that "a drinking water concentration of 4.0 mg F/L is considered to provide adequate protection for crippling skeletal fluorosis with a margin of safety" {U.S. EPA, 1985f, 6580525}.

EPA also published a secondary MCL (SMCL) of 2.0 mg/L to prevent the formation of cosmetically objectionable dental fluorosis (discoloration and/or pitting of teeth) in a significant portion of the population as a result of exposure to elevated drinking water fluoride levels, as EPA considered this adverse effect on public welfare that should be addressed under Section 1412c of the SDWA. EPA determined, based on epidemiological studies of dental fluorosis, that an SMCL of 2.0 mg/L of fluoride in drinking water would provide significant protection from dental caries and result in minimal occurrence of moderate to severe dental fluorosis {U.S. EPA, 1986d, 10634795}.

EPA did not assign a cancer descriptor to fluoride but determined that there was no evidence found in the available literature at the time to indicate that fluoride was carcinogenic {U.S. EPA, 1985f, 6580525}.

6.1.20.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for fluoride that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-59.

EPA is aware of ongoing efforts by the National Toxicology Program (NTP) to conduct a systematic review and meta-analysis of the published literature on developmental neurotoxicity for fluoride, see Appendix B for more information.

Table 6-59. Assessments Identified for Fluoride

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria {U.S. EPA, 1985f, 6580525}	–[d]	–	–	–	–	–[e]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1987s, 10186180}	0.06[f]	NOAEL	Hodge (1950, 2528292) cited in Underwood (1977, 8528)	–	–	–[g]
CalEPA PHG {CalEPA, 1997c, 10489819}	–[h]	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2003b, 192114}	0.05	NOAEL	Li et al. (2001, 2528303)	–	–	–
WHO GDWQ (WHO, 2004f, 10634794)	–[i]	–	–	–	–	–
EPA OW Dose-Response Analysis for Noncancer Effects {U.S. EPA, 2010d, 10493692}	**0.08[j]**	**BMDL**	**Dean et al. (1942, 10519160)**	–	–	–
HC GDWQ {HC, 2010a, 10528541}	0.105[k]	NOAEL	Dean et al. (1941, 10519237; 1942, 10519160)	–	–	–[l]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; BMDL = benchmark dose level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment did not calculate an oral reference value for fluoride but states that "the incidence of objectionable (moderate and severe) dental fluorosis is not consistently observed in a marked segment of the population until the drinking water concentration approaches 2.0 mg F/L" and "a drinking water concentration of 4.0 mg F/L is considered to provide adequate protection for crippling skeletal fluorosis with a margin of safety."

[e] This health assessment states that there is no valid evidence to classify fluoride as a potential carcinogen.

[f] The NOAEL of 1 ppm in drinking water was converted by EPA to the RfD of 0.06 mg/kg/day; uncertainty factors were not deemed necessary.

[g] This IRIS assessment did not evaluate the available evidence of human carcinogenic potential.

[h] This health assessment did not calculate an oral reference value for fluoride but reports a NOAEL of 1 mg/L (1 ppm) in drinking water for dental fluorosis in children {Dean, 1942, 10521195; CDC, 1991, 11264484; NRC, 1993, 10489881}; a total UF of 1 was applied to the NOAEL in the development of the CalEPA PHG.

[i] This health assessment did not calculate an oral reference value for fluoride but states that, in areas where total fluoride intakes are likely to approach or be greater than 6 mg/day, it would be appropriate to consider setting a drinking water guideline that is below a concentration of 1.5 mg/L.

[j] This RfD was calculated by summing the estimated fluoride doses from drinking water (0.07 mg/kg/day) and food (0.01 mg/kg/day) and is based on severe dental fluorosis in children. The estimated fluoride dose from drinking water was calculated using the BMDL drinking water fluoride level of 1.87 mg/L derived using data from Dean (1942, 10521195). Drinking water intake data came from the USDA 1977/1978 Nationwide Food Consumption Survey {Ershow and Cantor, 1989, 710071}, and estimated dietary fluoride intake data came from McClure (1943, 10510384). EPA's OW published a second document that provides fluoride exposure estimates for the age groups susceptible to severe dental fluorosis {U.S. EPA, 2010i, 10493698}.

[k] This TDI is based on prevention of moderate and severe dental fluorosis in children. It was developed using data from Dean et al. (1941, 10519237; 1942, 10519160) that show a drinking water fluoride level of 1.6 mg/L produced no moderate or severe dental fluorosis. HC converted the drinking water level to an estimated fluoride intake from drinking water of 98.5 µg/kg/day for a child 1–4 years old (based on daily fluoride intake data collected in the 1940s, a drinking water ingestion rate of 0.8 L/day for the 1-to-4-year-old age group, and a body weight of 13 kg for the 1-to-4-year-old age group). This value was added to 1940s-era estimated contributions of fluoride exposure from food (5.4 µg/kg/day assuming a 1940s diet for a 1-to-4-year-old child living in a community with 1.5 mg/L fluoride/L in drinking water), soil (1.19 µg/kg/day), and air (0.01 µg/kg/day) to yield a TDI of 105 µg/kg/day.

[l] This health assessment does not designate a cancer descriptor based on EPA's 2005 Guidelines for Carcinogen Risk Assessment but reports that fluoride is classified in Group VI (unclassifiable with respect to carcinogenicity in humans) in accordance with HC's classification scheme {HC, 1994a, 10528541}.

The health assessment selected for SYR 4 for fluoride is the EPA OW Dose-Response Analysis for Noncancer Effects {U.S. EPA, 2010d, 10493692} (bolded in Table 6-59) because this was the most recently published EPA health assessment that derives an oral toxicity value using the best available science including application of an updated modeling approach. Although a more recent health assessment was available (the HC GDWQ), it was based on the same critical study as the EPA OW Dose-Response Analysis for Noncancer Effects {Dean et al. 1942, 10519160} and relied on a NOAEL. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The EPA OW Dose-Response Analysis for Noncancer Effects identified an epidemiological study for fluoride in drinking water, Dean et al. (1942, 10519160), as the critical study to derive its toxicity value. The health assessment used BMD modeling to identify the POD using data from Dean et al. (1942, 10519160) and calculated a BMDL of 1.87 mg fluoride/L drinking water for severe dental fluorosis in children. The BMDL of 1.87 mg/L was considered as the concentration of fluoride in drinking water that led to severe dental fluorosis in children.

EPA then calculated the estimated fluoride dose that children would receive based upon drinking water with a concentration of 1.87 mg fluoride/L. These dose estimates incorporated several factors: age (from 0.5 to 14 years), estimated drinking water intake, and mean body weights. Drinking water intake data came from the USDA 1977/1978 Nationwide Food Consumption Survey {Ershow and Cantor, 1989, 710071}. EPA prepared a second document that provides fluoride exposure estimates for the age groups susceptible to severe dental fluorosis {U.S. EPA, 2010i, 10493698}. After considering the dose estimates for all the age groupings, EPA concluded that 0.07 mg/kg/day was the estimated RfD for fluoride in drinking water. EPA considered drinking water estimates below 0.07 mg/kg/day to be too close to the beneficial Institute of Occupational Medicine (IOM) recommended fluoride level of 0.05 mg/kg/day {IOM, 1997, 1326493}. EPA also included the estimated intake of fluoride from food into the total oral RfD, using the estimated dietary fluoride intake data from McClure (1943, 10510384). EPA subsequently estimated the oral RfD for fluoride by summing the estimated intake from drinking water (0.07 mg/kg/day) and the estimated intake from food (0.01 mg/kg/day). Thus, the total RfD for fluoride is 0.08 mg/kg/day. This RfD of 0.08 mg/kg/day is an estimate of the fluoride dose that is protective against severe dental fluorosis, while allowing for adequate fluoride exposure to prevent against tooth decay in children and adults {U.S. EPA, 2010d, 10493692}.

The total uncertainty factor (UF) for fluoride was 1. The reasons for not applying uncertainty factors for fluoride, at the time, include the beneficial protection against tooth decay observed at lower doses of fluoride, the POD was derived from a BMDL using data from a chronic human study of a sensitive population (i.e., children aged 6 months to 14 years), and EPA considered the database for fluoride toxicity to be complete {U.S. EPA, 2010d, 10493692}.

EPA has not completed a carcinogenicity assessment for fluoride {U.S. EPA, 1987s, 10186180}. Thus, there is no designation of a cancer descriptor based on EPA's 1986 or 2005 Guidelines for Carcinogen Risk Assessment However, one of the more recent assessments, the 2010 HC GDWQ {HC, 2010a, 10528541}, concluded that fluoride is "classified in Group VI —Unclassifiable with respect to carcinogenicity in humans." However, no CSFs were identified for fluoride.

6.1.20.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097} for the standard search. The start date of the standard SYR 4 literature search conducted in PubMed and Web of Science for fluoride was defined as one year prior to December 2015 resulting in a search date range from December 1, 2014 to February 10, 2022. For the standard search performed (i.e., conducted without specific health outcome search terms, similar to the other SYR 4 chemicals), 5,827 unique studies were identified following review of the literature. Following SWIFT-Review, 5,685 of the 5,827 unique studies were tagged to the evidence stream categories shown in Table 6-60.

From this literature search, 5,827 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One-hundred and forty-two of these 5,827 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 5,685 of the 5,827 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-60.

Table 6-60. Evidence Stream Heat Map Results for Fluoride Search[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,421
Environmental Fate	–	1,660
Human	All	220
	Epidemiologic Quantitative Analyses	3,536
In Vitro	–	1,759
No Tag	–	383
Total Unique Studies		**5,685**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

For fluoride, there was specific interest in capturing studies published between 2010 and 2014 on dental endpoints, including dental caries and fluorosis, because the SYR 3 literature search did not include search terms for dental toxicology endpoints. Therefore, for SYR 4, a targeted literature search using search terms for dental endpoints was conducted from January 2010 to December 2014, which is the interval between the EPA SYR 3 Summary {U.S. EPA, 2016c, 6557097} and the HC GDWQ {HC, 2010a, 10528541} and EPA OW Dose-Response Analysis for Noncancer Effects {U.S. EPA, 2010d, 10493692}, both conducted in 2010. For the targeted literature search performed, 1,696 unique studies were identified following review of the literature. Following SWIFT-Review, 1,690 of the 1,696 unique studies were tagged to the evidence stream categories shown in Table 6-61.

From this literature search, 1,696 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Six of these 1,696 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,690 of the 1,696 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-61.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for fluoride and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-61. Evidence Stream Heat Map Results for Fluoride Dental Toxicology Targeted Search[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	373
Environmental Fate	–	228
Human	All	1,467
	Epidemiologic Quantitative Analyses	109
In Vitro	–	367
No Tag	–	38
Total Unique Studies		**1,690**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

In addition to studies that assessed dental toxicity endpoints, EPA is aware of studies reporting an association between fluoride exposure and neurodevelopmental effects in the published literature (for more information, see Appendix B).

6.1.20.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-62 shows the comparison of the basis for the existing and potential MCLGs for fluoride.

Table 6-62. Comparison of the Basis for the Existing and Potential MCLGs for Fluoride

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b,c]	Potential MCLG[b,d]
Basis of Regulation										
EPA (1985f, 6580525)	–	–	–	–[e]	–	–	–	–	–	–
EPA (1985f, 6580525)	Shapiro (1983, 11264440); Koop (1984, 11264447); WHO (1984, (10606114 & 3978391)	Crippling skeletal fluorosis	–	–	–[f]	100%	General Population	70 kg adult, 2 L/day	4.0	–
Relevant Health Assessment Identified in SYR 4										
EPA (2010d, 10493692)	–	–	–	–[g]	–	–	–	–	–	–
EPA (2010d, 10493692)	Dean (1942, 10521195)	Severe dental fluorosis in children	–	–	0.08	40%[h]	Children aged 1– < 11 years	37.5 mL/kg/day[i]	–	0.9

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] EPA also published a secondary maximum contaminant level (SMCL) of 2.0 mg/L for fluoride to protect against dental fluorosis (an adverse cosmetic effect) (NPDWR for fluoride, April 2, 1986) {U.S. EPA, 1986d, 10634795}.

[d] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[e] EPA did not assign a cancer descriptor to fluoride but determined that there was no evidence found in the available literature at the time to indicate that fluoride was carcinogenic {U.S. EPA, 1985f, 6580525}.

[f] No RfD was derived. A POD of 20 mg/day (LOAEL) with a UF_H of 2.5 was used in the 1986 MCLG Regulation calculation. The RfV was derived as follows:
RfV = (20 mg/day)/(70 kg adult body weight)/(2.5 UF_H) = 0.11 mg/kg/day. The MCLG was calculated from the RfV as follows:
MCLG = (20 mg/day)/(70 kg adult body weight)/(2.5 UF_H) × (1.0 RSC) × (70 kg adult body weight)/(2 L/day adult drinking water intake) = 4.0 mg/L.

[g] EPA has not completed a carcinogenicity assessment for fluoride

[h] The selected RSC for SYR 4 is based on the analysis presented in Table 7-2 of EPA (2010i, 10493698).

[i] Drinking water intakes for children aged 1 to < 11 years calculated using https://fcid.foodrisk.org/percentiles# {JIFSAN, 2023, 10667059}.

6.1.20.5 SYR 4 Health Effects Conclusion

The existing NPDWR for fluoride was published on April 2, 1986 {U.S. EPA, 1986d, 10634795}. EPA set the MCLG at 4.0 mg/L based on an estimated 20 mg/day chronic fluoride intake, a human dose level at which adverse health effects of fluoride were not likely to occur {Shapiro, 1983, 11264440, U.S. EPA, 1985f, 6580525}. A cancer classification was not designated for fluoride at this time {U.S. EPA, 1985f, 6580525}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA OW Dose-Response Analysis for Noncancer Effects {U.S. EPA, 2010d, 10493692} to derive the potential MCLG because this was the most recently published EPA health assessment that derives an oral toxicity value using the best available science including application of an updated modeling approach. Based on an RfD of 0.08 mg/kg/day, an adjusted DWI-BW ratio of 37.5 mL/kg/day for children (age 1 to < 11 years) {JIFSAN, 2023, 10667059}, and an RSC of 40%, EPA calculated a potential MCLG of 0.9 mg/L. Because the life stage of 1 to < 11 years of age was identified as a specific developmental period of concern (i.e., potential critical window of exposure in the development of primary and most secondary teeth) in an EPA (2010d, 10493692) assessment based on dose-response data from a study by Dean (1942, 10521195), the potential MCLG was targeted to this age group. The RSCs presented in Table 7-2 {U.S. EPA, 2010i, 10493698} were based on fluoride intake data collected prior to the 2015 changes in the PHS recommendation for fluoridation of drinking water sources and FDA's recommended change in fluoride content in bottled water. In SYR 3 {U.S. EPA, 2016c, 6557097}, EPA acknowledged that the Table 7-2 (U.S. EPA, 2010i, 10493698) RSC estimates could change as a result of the 2015 PHS and FDA recommendations. For SYR 4, EPA has selected the RSC value of 40% as an estimate of the RSC for the 1 to < 11-year life stage because the 2010 RSC estimates are the best available estimates of fluoride relative source across the children's lifestages of concern that are available at this time.

Based on the analysis and conclusion presented the EPA OW Dose-Response Analysis for Noncancer Effects, a cancer classification was still not determined for fluoride. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 4 mg/L to the potential MCLG of 0.9 mg/L.

6.1.21 Heptachlor (CAS# 76-44-8 | DTXSID3020679)

6.1.21.1 Basis of the Existing MCLG

EPA published the current NPDWR for heptachlor on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987b, 10565929}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.0004 mg/L based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.1.21.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for heptachlor that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-63.

Table 6-63. Assessments Identified for Heptachlor

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985i, 94968}	0.0005	NOEL	Witherup et al. (1955, 10573402)[d]	4.5[e]	NCI (1977b, 64916)[f]; Davis (1965, 10534165) as evaluated by Reuber, (1977, 64922), cited in Epstein (1976, 62421)	B2[g]
EPA IRIS Chemical Assessment {U.S. EPA, 1987b, 10565929}	0.0005	NOEL	Velsicol Chemical Corporation (1955, 10573402)[d]	**4.5[e]**	**NCI (1977, 64916)[f]; Davis (1965, 10534165) as evaluated by Reuber (1977, 64922) cited in Epstein (1976, 62421)**	**B2[g]**
EPA OW Health Advisory {U.S. EPA, 1987t, 64929}	0.0005	NOEL	Witherup et al. (1955, 10573402)[d]	Refer to EPA OW Drinking Water Criteria	Refer to EPA OW Drinking Water Criteria	B2[g]
EPA OPP RED {U.S. EPA, 1992k, 10492398}	0.0005	NOEL	Witherup et al. (1955, 10573402)[d]	–	–	B2[g]
CalEPA PHG {CalEPA, 1999b, 10489837}	Refer to IRIS	Refer to IRIS	Refer to IRIS	4.1[h]	NCI (1977b, 64916)[f]; Davis (1965, 10534165)	Refer to IRIS
WHO GDWQ {WHO, 2004g, 10509444}	–	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2007c, 10489739}	0.0001[i]	LOAEL	Moser et al. (2001, 2526203); Smialowicz et al. (2001, 2526204)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOEL = no-observable-effect level; LEL = lowest effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value is bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the minimal risk level (MRL), population-adjusted dose (PAD), or reference dose (RfD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Velsicol Chemical Corporation (1955, 10573402) and Witherup et al. (1955, 10573402) appear to refer to the same study because they have the same publication year, the same experimental design and results, and because Witherup et al. (1955, 10573402) notes that it is an unpublished report to Velsicol Chemical Corporation.

[e] This CSF is the geometric mean of slope factors from four different mouse data sets.

[f] This study was performed with technical grade heptachlor (73% heptachlor, 22% trans-chlordane, 5% nonachlor).

[g] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[h] This estimate is the geometric mean of slope factors from three different mouse data sets that demonstrated an adequate fit of the polynomial equation to the data. This heath assessment considered the same four mouse data sets as the IRIS Chemical Assessment, but the geometric mean produced from using three of the four data sets produced the best fit. The slope factors

were derived using the LED_{10} (95% lower confidence limit on the dose that gives a 10% extra lifetime risk of cancer) and (body weight)$^{3/4}$ scaling. Additionally, to account for experiments with a duration of less than 2 years (lifespan typically assumed for rats and mice), an intercurrent mortality correction of about 1.5 for a study duration of 90 weeks ($(104/90)^3$) was applied.

[i] This oral reference value for heptachlor is an intermediate-duration MRL (no chronic-duration MRL was derived).

The health assessment selected for SYR 4 is the 1987 EPA IRIS Chemical Assessment {U.S. EPA, 1987b, 10565929} (bolded in Table 6-63) because it is an EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for heptachlor. Although there are more recent health assessments available, they either relied on the same critical studies as the EPA IRIS Chemical Assessment (e.g., EPA OW Health Advisory {U.S. EPA, 1987t, 64929}, CalEPA PHG {CalEPA, 1999b, 10489837}), or did not derive a cancer slope factor (e.g., EPA OPP RED {U.S. EPA, 1992b, 10492398}, WHO GDWQ {WHO, 2004g, 10509444}, and ATSDR Toxicological Profile {ATSDR, 2007c, 10489739}). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 1987 EPA IRIS assessment selected two critical studies {NCI, 1977b, 64916; Davis, 1965, 10534165} that served as the basis for determining the oral slope factor for heptachlor. The data from the study by Davis (1965, 10534165) were later reanalyzed by Reuber and Epstein {Reuber, 1977, 64922; Epstein, 1976, 62421}. Both critical studies were chronic studies that administered heptachlor via the diet to mice.

The study of Davis (1965, 10534165) fed C3H mice (100/sex/dose) a diet with 0 or 10 ppm heptachlor for two years. Health effects of decreased survival and increased incidence of benign liver lesions were reported. Reuber (1977, 64922) and Epstein (1976, 62421) reevaluated the histologic data from this study and reported a significant increase in liver carcinomas in the exposed male and female mice relative to controls. In the study by NCI (1977b, 64916), 50 B6C3F1 male and female mice were given feed containing technical-grade heptachlor at time-weighted average concentrations of 6.1 and 13.8 ppm and 9 and 18 ppm for males and females, respectively, for 80 weeks. Significant increases in hepatocellular carcinomas in high-dose males and females were reported {NCI, 1977b, 64916}.

The data obtained from the four data sets (male C3H mice; female C3H mice; male B56C3F1 mice; and female B56C3F1 mice) reported in the two critical studies {NCI, 1977b, 64916; Davis, 1965, 10534165} were used to calculate four individual cancer slope factors, which were determined using a linearized multistage procedure with extra risk analysis. The cancer slope factors were 12.4 and 14.9 $(mg/kg/day)^{-1}$ for C3H males and females, respectively, and 2.79 and 0.83 $(mg/kg/day)^{-1}$ for B6C3F1 males and females, respectively. The geometric mean of these four slope factors was calculated to derive an oral slope value of 4.5 $(mg/kg/day)^{-1}$ {U.S. EPA, 1987b, 10565929}.

Following the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, the 1987 EPA IRIS assessment determined that heptachlor is a B2 "probable human carcinogen," based on sufficient available evidence in animal models and because several structurally similar compounds are liver carcinogens {U.S. EPA, 1987b, 10565929}. Because heptachlor was classified as "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.21.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for heptachlor was defined as one year prior to December 2015, resulting in search date range from December 1, 2014 to March 8, 2022.

From this literature search, 482 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Sixteen of these 482 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 466 of the 482 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-64.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for heptachlor and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388 }).

Table 6-64. Evidence Stream Heat Map Results for Heptachlor[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	172
Environmental Fate	–	206
Human	All	272
	Epidemiologic Quantitative Analyses	16
In Vitro	–	122
No Tag	–	18
Total Unique Studies		**466**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.21.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-65 shows the comparison of the basis for the existing and potential MCLGs for heptachlor.

Table 6-65. Comparison of Existing and Potential MCLGs for Heptachlor

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation									
EPA (1987b, 10565929)	Davis (1965, 10534165); NCI (1977b, 64916)	Hepatocellular carcinomas	4.5	B2	–	General Population	70 kg adult, 2 L/day	0	–
Relevant Health Assessment Identified in SYR 4									
EPA (1987b, 10565929)	Davis (1965, 10534165); NCI (1977b, 64916)	Hepatocellular carcinomas	4.5	B2	–	General Population	33.8 mL/kg/ day	–	0

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[b] Values are expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.21.5 SYR 4 Health Effects Conclusion

The existing NPDWR for heptachlor was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987b, 10565929} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment {U.S. EPA, 1987b, 10565929} because it is an EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for heptachlor. Based on the analysis and conclusion presented in this health assessment, the cancer classification was maintained at B2. For heptachlor, the more recent information does not support a change to the MCLG.

6.1.22 Heptachlor epoxide (CAS# 1024-57-3 | DTXSID1024126)

6.1.22.1 Basis of the Existing MCLG

EPA published the current NPDWR for heptachlor epoxide on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2 {U.S. EPA, 1987c, 10317064}, "probable human carcinogen," according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.0002 mg/L, based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.1.22.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for heptachlor epoxide that were published prior to the cut-off date of November 2020, for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-66.

Table 6-66. Assessments Identified for Heptachlor Epoxide

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985i, 94968}	0.000013	LOEL	Kettering Laboratory, (1958, 10509758) as cited in EPA (1985i, 94968)[d]	9.1[e]	IRDC (1973, 62460)[f,g] as evaluated by Reuber (1977, 64922); Davis (1965, 10534165) as evaluated by Reuber (1977, 64922) cited in Epstein (1976, 62421)	B2[h]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1987c, 10317064}	0.000013	LEL	Dow Chemical (1958, 10509758)[d]	**9.1[e]**	**Velsicol Chemical Corporation (1973, 11264479)[f,g] as evaluated by Reuber (1977, 64922); Davis (1965, 10534165) as evaluated by Reuber (1977, 64922) cited in Epstein (1976, 62421)**	**B2[h]**
EPA OW Health Advisory {U.S. EPA, 1987t, 64929}	0.000013	LOEL	EPA (1985i, 94968)[d]	Refer to EPA OW Drinking Water Criteria	Refer to EPA OW Drinking Water Criteria	B2[h]
EPA OPP RED {U.S. EPA, 1992k, 10492398}	0.000013	LOEL	Witherup et al. (1958, 10573373)[d]	–	–	B2[h]
CalEPA PHG {CalEPA, 1999b, 10489837}	Refer to IRIS	Refer to IRIS	Refer to IRIS	5.5[i]	IRDC (1973, 62460)[f,g]; Davis (1965, 10534165)	Refer to IRIS
WHO GDWQ {WHO, 2004g, 10509444}	–	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2007c, 10489739}	–	–	–	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOEL = lowest-observed-effect level; LEL = lowest effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the minimal risk level (MRL), population-adjusted dose (PAD) or reference dose (RfD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on the same publication year, experimental details, and results, EPA assumed that the following citations all refer to the same study: Dow Chemical (1958, 10509758), EPA (1958, 10509758), Witherup et al. (1958, 10573373), and the study by Kettering Laboratory (1958, 10509758) cited in EPA (1977, 10509759).

[e] This CSF is the geometric mean of slope factors from four different mouse data sets.

[f] This study was performed with a 25:75 mixture of heptachlor:heptachlor epoxide.

[g] Based on the same publication year, experimental details, and results, EPA assumed that Velsicol Chemical Corporation (1973, 11264479) and IRDC (1973, 62460) refer to the same study.

[h] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[i] This CSF is the geometric mean of slope factors from four different mouse data sets. CSFs were derived using the LED_{10} (95% lower confidence limit on the dose that gives a 10% extra lifetime risk of cancer) and $(body\ weight)^{3/4}$ scaling.

The health assessment selected for SYR 4 is the EPA IRIS Chemical Assessment {U.S. EPA, 1987c, 10317064} (bolded in Table 6-66) because it is an EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for heptachlor epoxide. Although more recent health assessments were available, the EPA OW Health Advisory {U.S. EPA, 1987t, 64929} and the CalEPA PHG {CalEPA, 1999b, 10489837} relied on the same critical studies {NCI 1977b, 64916; Davis 1965, 10534165} as the EPA IRIS Chemical Assessment {U.S. EPA, 1987c, 10317064}. In addition, the EPA OPP RED {U.S. EPA, 1992k, 10492398}, WHO GDWQ {WHO, 2004g, 10509444}, and ATSDR Toxicological Profile {ATSDR, 2007c, 10489739} are more recent assessments, however, they did not derive a cancer slope factor. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the EPA IRIS Chemical Assessment, two critical studies were selected for a linearized multistage analysis to determine an oral slope factor {Velsicol Chemical Corporation, 1973, 11264479; Davis, 1965, 10534165}. These study data were later reanalyzed by Reuber and Epstein {Reuber, 1977, 64922; Epstein, 1976, 62421}. The two critical studies were a two-year mouse feed study {Davis, 1965, 10534165} and an 18-month chronic mouse study testing a 25:75 mixture of heptachlor:heptachlor epoxide {Velsicol Chemical Corporation, 1973, 11264479}.

Briefly, in the two-year feed study by Davis (1965, 10534165), C3H mice (100 mice/sex/dose) were fed diets containing 0 or 10 ppm heptachlor epoxide for two years. Decreased survival and increased benign liver lesions, which were later reassessed and determined to be increased liver carcinomas in {Reuber 1977, 64922; Epstein, 1976, 62421}, were observed in male and female mice dosed with 10 ppm.

In the study by Velsicol Chemical Corporation (1973, 11264479), a 25:75 heptachlor:heptachlor epoxide mixture was fed to CD-1 mice (100 mice/sex/dose) at dose levels of 0, 1, 5, or 10 ppm heptachlor epoxide for 18 months. Increased hyperplasia was observed at 5 and 10 ppm in both sexes, and these lesions were later determined to be liver carcinomas upon reevaluation by Reuber (1977, 64922).

The health effects data for male and female C3H and male and female CD-1 mice reported in these two critical studies {Velsicol Chemical Corporation, 1973, 11264479; Davis, 1965, 10534165} were used to calculate four individual cancer slope factors (male C3H mice; female C3H mice; male CD-1 mice; and female CD-1 mice). The four slope factors were derived using a linearized multistage procedure with extra risk (27.7 and 36.2 $(mg/kg/day)^{-1}$ for male and female C3H mice, respectively, and 1.04 and 6.48 $(mg/kg/day)^{-1}$ for CD-1 female and male mice, respectively). The geometric mean was calculated from these four slope factors to derive an oral slope value of 9.1 $(mg/kg/day)^{-1}$ {U.S. EPA, 1987c, 10317064}.

Based on the available information and following the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA determined that heptachlor epoxide is a B2 "probable human carcinogen" {U.S. EPA, 1987b, 10565929}. This determination was based on sufficient evidence of liver carcinomas in two strains of male and female mice {Davis, 1965, 10534165; Reuber, 1977, 64922; Epstein, 1976, 62421; Velsicol Chemical Corporation, 1973, 11264479} and structural similarity to other liver carcinogens {U.S. EPA, 1987c, 10317064}. Because heptachlor epoxide was classified as "probable human carcinogen" in 1987, the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.22.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for heptachlor epoxide was defined as one year prior to December 2015, resulting in a search date range from December 2014 to March 9, 2022.

From this literature search, 112 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two of these 112 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 110 of the 112 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-67.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for heptachlor and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-67. Evidence Stream Heat Map Results for Heptachlor Epoxide[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	37
Environmental Fate	–	47
Human	All	76
	Epidemiologic Quantitative Analyses	4
In Vitro	–	21
No Tag	–	1
Total Unique Studies		**110**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.22.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-68 shows the comparison of the basis for the existing and potential MCLGs for heptachlor epoxide.

Table 6-68. Comparison of Existing and Potential MCLGs for Heptachlor Epoxide

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation									
EPA (1987c, 10317064)	Davis (1965, 10534165); Velsicol Chemical Corporation (1973, 11264479)	Hepatocellular carcinomas	9.1	B2	–	General Population	70 kg adult, 2 L/day	0	–
Relevant Health Assessment Identified in SYR 4									
EPA (1987c, 10317064)	Davis (1965, 10534165); Velsicol Chemical Corporation (1973, 11264479)	Hepatocellular carcinomas	9.1	B2	–	General Population	33.8 mL/kg/ day	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[b] Values are expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.22.5 SYR 4 Health Effects Conclusion

The existing NPDWR for heptachlor epoxide was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on the 1987 health assessment's cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1987c, 10317064} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment {U.S. EPA, 1987c, 10317064} because it is an EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for heptachlor epoxide. Based on the analysis and conclusion presented in this health assessment, the cancer classification was maintained at B2, "probable human carcinogen." For heptachlor epoxide, the more recent information does not support a change to the MCLG.

6.1.23 Hexachlorobenzene (CAS# 118-74-1 | DTXSID2020682)

6.1.23.1 Basis of the Existing MCLG

EPA published the current NPDWR for hexachlorobenzene on July 17, 1992, establishing an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1992g, 10587719} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.001 mg/L, based on analytical feasibility {U.S. EPA, 1992g, 10587719}.

6.1.23.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for hexachlorobenzene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-69.

Table 6-69. Assessments Identified for Hexachlorobenzene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987u, 5926062}	0.0008	NOAEL	Arnold et al. (1985, 63199)	–	–	B2[d]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991g, 10256180}[e]	0.0008	NOAEL	Arnold et al. (1985, 63199)	1.6	Erturk et al. (1986, 63064)	B2[d]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1991h, 4296103}	0.0008	NOAEL	Arnold et al. (1985, 63199)	1.7	Lambrecht et al. (1983a, 5926019); Lambrecht et al. (1983b, 5926018)	B2[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG {CalEPA, 2003d, 10489846}	0.00003[f]	LOAEL	Arnold et al. (1985, 63199)	1.09[g]	Arnold et al. (1985, 63199)	Refer to IRIS
WHO GDWQ {WHO, 2004b, 1239468}	–[h]	–	–	–[h]	–	–
EPA OPP RED Document {U.S. EPA, 2008b, 1593840}	–	–	–	**1.02[i]**	**–**	**B2[d]**
EPA ORD PPRTV {U.S. EPA, 2010j, 1260380}	Refer to IRIS[j]	–	–	Refer to IRIS	–	Refer to IRIS
ATSDR Toxicological Profile {ATSDR, 2015c, 4322480}	0.00007[k]	LOAEL	Arnold et al. (1985, 63199)	–	–	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the point of departure/uncertainty factor (POD/UF), reference dose (RfD), minimal risk level (MRL), or health-based guidance value.

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] Oral RfD last revised 1988; carcinogenicity assessment last revised 1991.

[f] POD/UF calculated by CalEPA based on a POD of 0.01 mg/kg/day and a UF of 300.

[g] The human CSF of 1.09 $(mg/kg/day)^{-1}$ was based on pheochromocytomas in female rats from Arnold et al. (1985, 63199); a human cancer potency estimate (q1*) of 1.294 $(mg/kg/day)^{-1}$ based on pheochromocytomas in female rats from Lambrecht et al. (1983a, 5926019; 1983b, 5926018) was also calculated by CalEPA. Two separate PHG values were calculated using these two values and results were averaged to establish the final PHG.

[h] This health assessment did not derive an oral RfV or CSF but reports a health-based guidance value of 0.00016 mg/kg/day that was derived by WHO (1997, 1518932) using the TD_{05} approach, where TD_{05} is defined as the intake or exposure associated with a 5% excess incidence of tumors in experimental studies in animals.

[i] The CSF of 1.02 $(mg/kg/day)^{-1}$ was calculated using the rat hepatocellular carcinoma data from the IRIS database {U.S. EPA, 1991g, 10256180} and was modified by 0.6× to apply EPA's (body weight)3/4 scaling factor {U.S. EPA, 2008b, 1593840}.

[j] A chronic provisional-RfD (p-RfD) was not derived because the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991g, 10256180} reports an RfD based on chronic exposure. A subchronic p-RfD of 0.00001 mg/kg/day was derived based on degenerative changes in primary ovarian follicles of female Cynomolgus monkeys exposed to hexachlorobenzene for 13 weeks {Bourque, 1995, 652172}.

[k] The chronic MRL is based on the same critical study, Arnold et al. (1985, 63199), that was used by EPA; however, the ATSDR MRL was based on a different endpoint (peribiliary lymphocytosis and fibrosis of the liver) than the endpoint selected in the EPA health assessments (hepatic centrilobular basophilic chromogenesis).

The hexachlorobenzene health assessment selected for SYR 4 is the OPP RED Document for Pentachlorophenol, which contains a risk assessment for hexachlorobenzene {U.S. EPA, 2008b, 1593840}, (bolded in Table 6-69) because it used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for hexachlorobenzene Although the more recent EPA ORD PPRTV {U.S. EPA, 2010j, 1260380} and ATSDR Toxicological Profile {ATSDR, 2015c, 4322480} were available, they referenced the oral CSF and/or cancer descriptor derived by the selected EPA OPP RED Document {U.S. EPA, 2008b, 1593840}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

OPP derived a CSF for hexachlorobenzene by modifying the CSF reported in the IRIS Chemical Assessment Summary {U.S. EPA, 1988g, 10256180}. The CSF reported in the IRIS Chemical Assessment Summary is 1.6 $(mg/kg/day)^{-1}$ based on hepatocellular carcinomas in female Sprague-Dawley rats observed in a study by Erturk et al. (1986, 63064). Erturk et al. (1986, 63064) fed Sprague-Dawley rats (94 rats/sex/dose) a diet of 0, 75, or 150 ppm hexachlorobenzene for up to two years. Dosed animals of both sexes showed increased incidence of liver and renal tumors after 12 months; female rats had a statistically significant increase in hepatocellular carcinomas. The 1988 IRIS Chemical Assessment Summary used an animal to human scaling factor of 2/3, but newer health assessments now use a scaling factor of ¾ for deriving CSFs ($(bodyweight)^{3/4}$). Thus, OPP adjusted for $(bodyweight)^{3/4}$ by modifying the CSF value from IRIS by 0.6, resulting in a CSF of 1.02 $(mg/kg/day)^{-1}$ {U.S. EPA, 2008b, 1593840}.

EPA classified hexachlorobenzene as a Group B2 "probable human carcinogen" {U.S. EPA, 2008b, 1593840; U.S. EPA, 1991g, 10256180} under EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on inadequate human evidence and animal evidence that showed tumors in liver, thyroid, and kidney in three rodent species (rats, mice, and hamsters) following oral exposure. Because hexachlorobenzene is classified as a "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.23.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the ATSDR Toxicological Profile was used to assign the date limit {ATSDR, 2015c, 4322480}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for hexachlorobenzene was defined as one year prior to December 2015, resulting in search date range from December 1, 2014 to March 10, 2022. From this literature search, 794 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Fourteen of these 794 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 780 of the 794 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-70.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for hexachlorobenzene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-70. Evidence Stream Heat Map Results for Hexachlorobenzene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	20
Environmental Fate	–	296
Human	All	430
	Epidemiologic Quantitative Analyses	20
In Vitro	–	191
No Tag	–	20
Total Unique Studies		**780**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.23.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-71 shows the comparison of the basis for the existing and potential MCLGs for hexachlorobenzene.

Table 6-71. Comparison of the Basis for the Existing and Potential MCLGs for Hexachlorobenzene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1992g, 10587719)	–	–	–	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA OPP (2008b, 1593840)	Erturk et al. (1986, 63064)	Hepatocellular carcinomas in rats	1.02	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.23.5 SYR 4 Health Effects Conclusion

The existing NPDWR for hexachlorobenzene was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on a cancer classification of B2, "probable human carcinogen" according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero {U.S. EPA, 1992g, 10587719}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the OPP RED Document for Pentachlorophenol {U.S. EPA, 2008b, 1593840} (which contains an assessment of hexachlorobenzene) because it used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. Based on the analysis and conclusion presented in the 2008 OPP risk assessment, the cancer classification for hexachlorobenzene was maintained at B2. For hexachlorobenzene, more recent information does not support a change to the MCLG.

6.1.24 Hexachlorocyclopentadiene (CAS# 77-47-4 | DTXSID2020688)

6.1.24.1 Basis of the Existing MCLG

EPA published the NPDWR for hexachlorocyclopentadiene on July 17, 1992 {U.S. EPA, 1992g, 10587719}, establishing both an MCL and MCLG of 0.05 mg/L. The MCLG of 0.05 mg/L was derived from an RfD of 0.007 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991i, 10509462} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.24.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for hexachlorocyclopentadiene that were published prior to the cut-off date of November 2020, for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-72.

Table 6-72. Assessments Identified for Hexachlorocyclopentadiene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria {U.S. EPA, 1991i, 10509462}	0.007	$NOAEL_{adj}$	Southern Research Institute (1981, 5908540); Abdo et al. (1984, 13631)	–	–	D[d]
ATSDR Toxicological Profile {ATSDR, 1999, 13633}	0.1[e]	NOAEL	Abdo et al. (1984, 13631)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2001c, 10509468}	**0.006[f]**	**$BMDL_{10}$**	**Abdo et al. (1984, 13631)**	–	–	E[d,g]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG {CalEPA, 2018b, 10489857}	0.0011	$BMDL_{05\text{-}adj}$	Abdo et al. (1984, 13631)	–	–	–

Notes: POD = point of departure; CSF = cancer slope factor; $NOAEL_{adj}$ = NOAEL adjusted by a factor of 5/7 to account for discontinuous exposure (5 days/7 days); dash (–) = not provided; NOAEL = no-observed-adverse-effect level; $BMDL_{05\text{-}adj}$ = benchmark dose lower bound where the change in response is likely to be smaller than 5%, adjusted by a factor of 5/7 to account for discontinuous exposure (5 days/7 days); $BMDL_{10}$ = benchmark dose lower bound, where the change in response is likely to be smaller than 10%.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily dose (ADD), minimal risk level (MRL), or reference dose (RfD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] This is an intermediate-duration oral MRL. A chronic-duration oral MRL was not derived because no data were located on the effects of chronic oral exposure to hexachlorocyclopentadiene in humans or animals. Doses were normalized to account for 5 days/week exposure, and a UF of 100 was applied.

[f] This chronic oral RfD is based on a subchronic (13-week) oral toxicity study; a UF of 1,000 was applied.

[g] Group E determination was based on no evidence of carcinogenicity in humans by the inhalation route based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}; the IRIS Chemical Assessment Summary states that the potential for carcinogenicity by the oral route is indeterminate.

The health assessment selected for SYR 4 is the 2001 EPA IRIS Chemical Assessment {U.S. EPA, 2001c, 10509468} (bolded in Table 6-72) because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. While more current health assessments of non-cancer endpoints for hexachlorocyclopentadiene were available, including the CalEPA PHG (2014, 10489858), those health assessments did not introduce new science (i.e., did not use a newer critical study than the critical study used in the EPA IRIS Chemical Assessment) {U.S. EPA, 2001c, 10509468}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals).

In this health assessment, EPA selected Abdo et al. (1984, 13631) to derive a chronic oral toxicity value for hexachlorocyclopentadiene. In this subchronic study, F344 rats (10/sex/group) were administered hexachlorocyclopentadiene via oral gavage 5 days/week for 13 weeks at doses of 0, 10, 19, 38, 75, or 150 mg/kg/day. Chronic stomach irritation, manifested by forestomach lesions, was chosen as the critical effect, and EPA used these data to conduct BMD modeling. EPA determined that the benchmark dose lower limit ($BMDL_{10}$) for chronic forestomach irritation was 6 mg/kg/day. A total UF of 1,000 was applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, 3 for extrapolation from subchronic to chronic exposure, and 3 for database deficiencies due to lack of reproductive studies. After applying the total UF, the oral RfD was calculated to be 0.006 mg/kg/day {U.S. EPA, 2001c, 10509468}.

The 2001 EPA IRIS Chemical Assessment concluded that the available chronic health effect data in both human and animals are lacking studies via the oral route of exposure for hexachlorocyclopentadiene, thus the potential for carcinogenicity by the oral route is indeterminate {U.S. EPA, 2001c, 10509468}. EPA has categorized hexachlorocyclopentadiene as Group E, "evidence of non-carcinogenicity for humans" via the inhalation route based on the lack of human and animal carcinogenicity according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.24.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the CalEPA PHG assessment was used to assign the date limit {CalEPA, 2018b, 10489857}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for hexachlorocyclopentadiene was defined as one year prior to December 2015 resulting in a search date range from December 1, 2014 to March 18, 2022.

From this literature search, 50 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 50 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 49 of the 50 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-73.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for hexachlorocyclopentadiene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-73. Evidence Stream Heat Map Results for Hexachlorocyclopentadiene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	11
Environmental Fate	–	5
Human	All	31
	Epidemiologic Quantitative Analyses	2
In Vitro	–	17
No Tag	–	7
Total Unique Studies		**49**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.24.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-74 shows the comparison of the basis for the existing and potential MCLGs for hexachlorocyclopentadiene.

Table 6-74. Comparison of the Basis for the Existing and Potential MCLGs for Hexachlorocyclopentadiene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1991i, 10509462)	–	–	–	D	–	–	–	–	–	–
EPA (1991i, 10509462)	Southern Research Institute (1981, 5908540); Abdo et al. (1984, 13631)	Irritation to portals of exposure (gavage)	–	–	0.007	20%	General Population	70 kg adult, 2 L/day	0.05	–
Relevant Assessment Identified in SYR 4										
EPA (2001c, 10509468)	–	–	–	E[d]	–	–	–	–	–	–
EPA (2001c, 10509468)	Abdo et al. (1984, 13631)	Irritation to portals of exposure (gavage)	–	–	0.006	20%	General Population	33.8 mL/ kg/day	–	0.04

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values are expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] Group E determination was based on no evidence of carcinogenicity in humans by the inhalation route; the IRIS Chemical Assessment Summary states that the potential for carcinogenicity by the oral route is indeterminate.

6.1.24.5 SYR 4 Health Effects Conclusion

The existing NPDWR for hexachlorocyclopentadiene was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.007 mg/kg/day {U.S. EPA, 1991i, 10509462}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg) and an RSC of 20%, EPA set the MCLG at 0.05 mg/L and assigned hexachlorocyclopentadiene a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991i, 10509462}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment {U.S. EPA, 2001c, 10509468} to derive the potential MCLG because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.006 mg/kg/day {U.S. EPA, 2001c, 10509468}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.04 mg/L. Based on the analysis and conclusion presented in the 2001 EPA health assessment, the cancer classification was updated to E, "evidence of non-carcinogenicity for humans" via the inhalation route, in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The potential for carcinogenicity by the oral route is indeterminant{U.S. EPA, 2001c, 10509468}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.05 mg/L to the potential MCLG of 0.04 mg/L.

6.1.25 Lindane (CAS# 58-89-9 | DTXSID2020686)

6.1.25.1 Basis of the Existing MCLG

EPA published the current NPDWR for lindane on January 30, 1991, establishing both an MCLG and an MCL of 0.0002 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.0003 mg/kg/day {U.S. EPA, 1988i, 10532466} and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1988i, 10532466}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.25.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for lindane that were published prior to the cut-off date of November 2020, for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-75.

Table 6-75. Assessments Identified for Lindane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1987v, 10255206}	0.0003	NOAEL	RCC (1983, 10529401)[d]	–	–	–
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	0.0003	NOAEL	RCC (1983, 10529401)[d]	–	–	B2/C[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988i, 10532466}	0.0003	NOAEL	RCC (1983, 10529401)[d]	1.3	Thorpe and Walker (1973, 1260438)	B2/C[e]
EPA OPP HHRA {U.S. EPA, 2002i, 10492445}	0.0016[f]	NOAEL	Amyes (1989, 10534152; 1990, 6836770	–	–	S[g]
EPA OPP RED {U.S. EPA, 2004a, 10492448}	**0.0016[f]**	**NOAEL**	**Amyes (1989, 10534152; 1990, 6836770)**	–	–	S[g]
WHO GDWQ {WHO, 2004h, 10509445}	0.005	NOAEL	Not Reported[h]	–	–	–[i]
CalEPA PHG {CalEPA, 2005b, 10489839}[j]	–[j]	–	–	1.1	Thorpe and Walker (1973, 1260438)	–
ATSDR Toxicological Profile {ATSDR, 2005a, 10259529}	0.00001[k]	LOAEL	Meera et al. (1992, 65855)	–	–	–[l]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), population-adjusted dose (PAD), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] RCC (1983, 10529401) and a 1983 reference cited in the EPA IRIS Chemical Assessment Summary with "Zoecon Corp." as author appear to be the same study because they describe the same model (Wistar KFM-Han (outbred) SPF rats), dosing paradigm (0, 0.2, 0.8, 4, 20, or 100 ppm lindane (99.85%) in the diet for 12 weeks), and the same treatment-related effects (liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular distension, interstitial nephritis, and basophilic tubules) at the same NOAEL (4 ppm).

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}; this health assessment concludes that the cancer classification for lindane falls somewhere between Group B2 and Group C.

[f] A 3× FQPA safety factor was applied to the chronic RfD to derive this chronic Population Adjusted Dose (cPAD).

[g] Based on EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999a, 41631}. Classification based on an increased incidence of benign tumors only. Therefore, the OPP/Cancer Assessment Review Committee (CARC) determined that the quantification of human cancer risk is not required.

[h] The ADI established by JMPR (2002, 6591483) was based on a 2-year study of toxicity and carcinogenicity in rats. The reference is not reported in WHO (2004h, 10509445) or JMPR (2002, 6591483), but it appears to be the same study as Amyes (1989, 10534152; 1989, 6836770) based on the study descriptions and the reported effects at the LOAEL.

[i] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment but states that "in the absence of genotoxicity and on the basis of the weight of the evidence from the studies of carcinogenicity, the Meeting concluded that lindane is not likely to pose a carcinogenic risk to humans."

[j] CalEPA's PHG for lindane was established in 1999 but the original health assessment was not available on CalEPA's website at the time of this review. The 2005 memorandum provides an update on the lindane literature and a summary of CalEPA's re-evaluation of the PHG. The 2005 re-evaluation confirmed the 1999 PHG derivation and the value was not changed. The memo does not report a noncancer oral reference value for lindane.

[k] Intermediate-duration oral MRL; ATSDR did not derive a chronic oral MRL due to insufficient data.

[l] This health assessment did not provide a cancer descriptor but reported that EPA has classified lindane as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential," citing EPA (2001d, 628259) and EPA (2002i, 10492445).

The health assessment selected for SYR 4 is the 2004 EPA OPP RED {U.S. EPA, 2004a, 10492448} (bolded in Table 6-75) because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk and derivation of an oral RfD. More recent health assessments for lindane were available, however they either did not introduce a new critical study (e.g., WHO GDWQ (2004h, 10509445)), or did not derive a relevant toxicity value (e.g., CalEPA PHG (2005b, 10489839), ATSDR Toxicological Profile (2005a, 10259529)). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2004 EPA OPP RED selected a chronic study described in two unpublished papers by Amyes (1990, 6836770) and Amyes (1989, 10534152) as the critical study for the lindane POD. In this two-year chronic oral toxicity study, Wistar rats (115/sex/dose) were exposed to lindane via diet (0, 1, 10, 100, or 400 ppm) for 104 weeks. The corresponding calculated delivered doses were 0, 0.05, 0.47, 4.81, and 19.66 mg/kg/day, respectively, for males and 0, 0.06, 0.59, 6.00, and 24.34 mg/kg/day, respectively, for females. Interim results at 26 weeks were reported in Amyes (1989, 10534152). Decreased platelets, increased liver and spleen weights, and histological changes in the liver (i.e., periacinar hepatocyte hypertrophy) were observed at the LOAEL of 100 ppm, (4.81 mg/kg/day for male rats and 6.0 mg/kg/day for female rats) {U.S. EPA, 2004a, 10492448}. The reported NOAEL for this chronic dietary rat study is 10 ppm, or 0.47 and 0.59 mg/kg/day for males and females, respectively, and the NOAEL of 0.47 mg/kg/day for male rats was selected as the POD {U.S. EPA, 2004a, 10492448}. A total uncertainty factor (UF) of 100 was applied: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 3 for the protection of infants and children due to animal evidence observed in developmental neurotoxicity and reproduction studies, the chronic population-adjusted dose (cPAD) was calculated to be 0.0016 mg/kg/day {U.S. EPA, 2004a, 10492448}.

EPA reported that lindane has "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" {U.S. EPA, 2004a, 10492448} according to EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631} based on an increased incidence of benign tumors in animals. The HED Cancer Assessment Review Committee (CARC), therefore, recommended that the quantification of human cancer risk is not required {U.S. EPA, 2004a, 10492448}.

6.1.25.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for lindane was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 23, 2022. From this literature search, 1,132 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty-nine of these 1,132 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,103 of the 1,132 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-76.

Table 6-76. Evidence Stream Heat Map Results for Lindane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	348
Environmental Fate	–	525
Human	All	598
	Epidemiologic Quantitative Analyses	34
In Vitro	–	305
No Tag	–	34
Total Unique Studies		**1,103**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.25.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-77 shows the comparison of the basis for the existing and potential MCLGs for lindane.

Table 6-77. Comparison of the Basis for the Existing and Potential MCLGs for Lindane

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1988i, 10532466)	Thorpe & Walker (1973, 1260438)	Oncogenic effects observed in the liver	1.3	C	–	–	–	–	–	–
EPA (1988i, 10532466)	RCC (1983, 10529401)	Liver, kidney toxicity	–	–	0.0003	20%	General Population	70 kg adult, 2 L/day	0.0002	–
Relevant Health Assessment Identified in SYR 4										
EPA (2004a, 10492448)	–	–	–	S	–	–	–	–	–	–
EPA (2004a, 10492448	Amyes (1989, 10534152; 1990, 6836770)	Hepatocyte hypertrophy, increased liver weight, and decreased platelets in rats	–	–	0.0016[d]	20%	General Population	33.8 mL/kg/ day	–	0.009

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] Canceled by EPA OPP {U.S. EPA, 2006d, 11264441}. The chronic PAD that incorporates the FQPA factor is reported here.

6.1.25.5 SYR 4 Health Effects Conclusion

The existing NPDWR for lindane was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.0003 mg/kg/day {U.S. EPA, 1988i, 10532466}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.0002 mg/L and assigned lindane a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1988i, 10532466; U.S. EPA, 1991a, 5499}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA OPP RED {U.S. EPA, 2004a, 10492448} to derive the potential MCLG because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk and derived an oral chronic RfD. Based on a PAD of 0.0016 mg/kg/day {U.S. EPA, 2004a, 10492448}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.009 mg/L. Based on the analysis and conclusion presented in the EPA OPP RED, EPA updated the cancer classification to S, "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential," in accordance with EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}. EPA concluded that new health effects information supports raising the current MCLG of 0.0002 mg/L to the potential MCLG of 0.009 mg/L.

6.1.26 Methoxychlor (CAS# 72-43-5 | DTXSID9020827)

6.1.26.1 Basis of the Existing MCLG

EPA published the current NPDWR for methoxychlor on January 30, 1991, establishing both an MCLG and an MCL of 0.04 {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.005 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1987w, 63608}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.26.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for methoxychlor that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-78.

Table 6-78. Assessments Identified for Methoxychlor

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987x, 11311299}	0.05	NOAEL	Lehman (1965, 3381275)	–	–	–
EPA OW Drinking Water Criteria {U.S. EPA, 1987w, 63608}	0.005	NOAEL	Kincaid Enterprises (1986, 10524695)[d]	–	–	D[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1993b, 10307066}	0.005	NOEL[f]	Kincaid Enterprises (1986, 10524695)[d]	–	–	D[e]
EPA OPP RED {U.S. EPA, 2004d, 10492446}	–	–	–	–	–	–
WHO GDWQ {WHO, 2004i, 10509446}	0.005	NOAEL	Kincaid Enterprises (1986, 10524695)[d]	–	–	–
CalEPA PHG {CalEPA, 2010e, 10489852}	**0.00002**	**LOAEL**	**Judy et al. (1999, 1308996)**	–	–	–
ATSDR Toxicological Profile and Addendum {ATSDR, 2002b, 3378220; 2012c, 10489751}	0.005[g]	LOAEL	Chapin et al. (1997, 758106)	–	–	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOEL = no-observed-effect level; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The critical study was cited as Kincaid Enterprises Inc. (1986, 10524695) in EPA (1993b, 10307066), Trutter (1986, 10524695) in EPA (1987w, 63608), and Hazleton Laboratories Inc., Kincaid Enterprises Inc. (1986, 10524695) in WHO (2004i, 10509446). Based on the same publication year, experimental design, and results, EPA assumes that all of these citations refer to the same study.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The oral RfD is based on a NOEL of 5.01 mg/kg/day and a UF of 1000. This 5.01 mg/kg/day value is referred to as a NOAEL in EPA (1987w, 63608) and WHO (2004i, 10509446).

[g] This is an intermediate-duration oral MRL based on accelerated onset of puberty in immature female rats that had been exposed in utero, during lactation, and after weaning. ATSDR (2002b, 3378220; 2012c,10489751) did not derive a chronic oral MRL due to inadequate data.

The health assessment selected for SYR 4 is the 2010 CalEPA PHG {CalEPA, 2010e, 10489852} (bolded in Table 6-78) because it derived a relevant toxicity value based on the most recent critical study. Although a more recent health assessment for methoxychlor exists, the 2012 addendum to the 2002 ATSDR Toxicological Profile {ASTDR, 2002b, 3378220; ATSDR 2012c, 10489751}, it does not derive a chronic duration toxicity value. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The 2010 CalEPA assessment selected Judy et al. (1999, 1308996) as the critical study for methoxychlor. This study dosed pregnant CF-1 mice via oral gavage with 0, 0.02, or 2 mg/kg/day methoxychlor in corn oil during gestational days (GD) 11–17. The offspring were followed to adulthood to observe effects. At

both methoxychlor dose levels, the 9.5-month-old adult male offspring were observed to have decreased relative liver weights and increased relative prostate weights compared to controls. Based on these critical effects, the LOAEL for this study is 0.02 mg/kg/day, the lowest dose tested. A total uncertainty factor (UF) of 1,000 was applied: 10 for interspecies variability, 10 for intraspecies variability, and 10 for extrapolation of POD from a LOAEL. After applying the total UF, the acceptable daily dose (ADD) was calculated to be 0.00002 mg/kg/day {CalEPA, 2010e, 10489852}.

Following the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, the EPA NPDWR determined methoxychlor as "not classified as to human carcinogenicity" based on unavailable human data and inconclusive animal evidence, which corresponds to a Group D cancer classification {U.S. EPA, 1993b, 10307066}.

6.1.26.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for methoxychlor was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 9, 2022.

From this literature search, 152 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two of these 152 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 150 of the 152 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-79.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for methoxychlor and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-79. Evidence Stream Heat Map Results for Methoxychlor[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	86
Environmental Fate	–	48
Human	All	89
	Epidemiologic Quantitative Analyses	2
In Vitro	–	69
No Tag	–	3
Total Unique Studies		**150**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.26.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-80 shows the comparison of the basis for the existing and potential MCLGs for methoxychlor.

Table 6-80. Comparison of the Basis for the Existing and Potential MCLGs for Methoxychlor

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987w, 63608)	–	–	–	D	–	–	–	–	–	–
EPA (1987w, 63608)	Kincaid Enterprises (1986, 10524695)	Excessive loss of litters, decreased body weight	–	–	0.005	20%	General Population	70 kg adult, 2 L/day	0.04	–
Relevant Health Assessment Identified in SYR 4										
EPA (1993b, 10307066)	–	–	–	D	–	–	–	–	–	–
CalEPA (2010e, 10489852)	Judy et al. (1999, 1308996)	Increased prostate, seminal vesicle weight; decreased liver weight in adult male offspring	–	–	0.00002	20%	General Population	33.8 mL/kg/ day	–	0.0001

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.26.5 SYR 4 Health Effects Conclusion

The existing NPDWR for methoxychlor was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.005 mg/kg/day {U.S. EPA, 1987w, 63608}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.04 mg/L and assigned methoxychlor a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1993b, 10307066}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the CalEPA PHG {CalEPA, 2010e, 10489852} to derive the potential MCLG because it derived a relevant toxicity value based on the most recent critical study. Based on an RfD of 0.00002 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.0001 mg/L. Based on the analysis and conclusion presented in the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1993b, 10307066}, the most recent health assessment of carcinogenic potential, the cancer classification for methoxychlor was maintained as D, "not classifiable as to human carcinogenicity." EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.04 mg/L to the potential MCLG of 0.0001 mg/L.

6.1.27 Nitrate (as N) (CAS# 14797-55-8 | DTXSID5024217)

6.1.27.1 Basis of the Existing MCLG

EPA published the current NPDWR for nitrate on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established both an MCLG and an MCL of 10 mg/L (as nitrogen (N)). EPA based the MCLG on a survey of epidemiologic studies of infant methemoglobinemia in populations exposed to nitrate contaminated water {U.S. EPA, 1990a, 10492389}. No cancer classification is available for nitrate {U.S. EPA, 1990a, 10492389; U.S. EPA, 1991b, 10293342}.

6.1.27.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for nitrate that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-81.

Table 6-81. Assessments Identified for Nitrate

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria {U.S. EPA, 1990a, 10492389}	1.6 (as nitrate-N)[d]	NOAEL	Bosch et al. (1950, 3841331); Walton (1951, 3002705)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991b, 10293342}	**1.6 (as nitrate-N)**	**NOAEL**	**Bosch et al. (1950, 3841331); Walton (1951, 3002705)**	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1993c, 10492400}	1.6 (as nitrate-N)	NOAEL	Bosch et al. (1950, 3841331); Walton (1951, 3002705)	–	–	–
HC GDWQ {HC, 2013b, 3603664}	–[e]	–	–	–	–	–
WHO GDWQ {WHO, 2016b, 3859520}	–[f]	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2017a, 3980254}	4 (as nitrate) 1 (as nitrate-N)[g]	NOAEL	Walton (1951, 3002705)	–	–	–
CalEPA PHG {CalEPA, 2018b, 10489857}	13.2 (as nitrate) 3 (as nitrate-N)[h]	NOAEL	Bosch et al. (1950, 3841331); Walton (1951, 3002705); Sadeq et al. (2008, 867021)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Nitrate is normally expressed as the amount of nitrogen within the nitrate molecule commonly shown as mg nitrate-nitrogen/L.

[e] HC (2013b, 3603664) did not derive an oral reference value for nitrate but instead relied on a drinking water NOAEL of 45 mg/L as nitrate (10 mg/L as nitrate-N) based on the weight of evidence from human studies to establish a drinking water health-based value (HBV) for nitrate.

[f] WHO (2016b, 3859520) did not derive an oral reference value for nitrate but instead relied on a drinking water NOAEL of 50 mg/L as nitrate (11 mg/L as nitrate-N) based on the weight of evidence from human studies to establish a drinking water guideline value for nitrate.

[g] ATSDR (2017a, 3980254) derived an MRL of 4 mg/kg/day as nitrate (rounded from 4.33 mg/kg/day). The MRL was converted by EPA to 1 mg/kg/day as nitrate-N using the unrounded value (4.33 mg/kg/day) and a conversion factor (1 mg nitrate = 0.226 mg nitrate-N).

[h] CalEPA (2018b, 10489857) derived an ADD of 13.2 mg/kg/day as nitrate that was converted by EPA to 3 mg/kg/day as nitrate-N using a conversion factor (1 mg nitrate = 0.226 mg nitrate-N).

The health assessment selected for SYR 4 is the 1991 EPA IRIS Chemical Assessment {U.S. EPA, 1991b, 10293342} (bolded in Table 6-81) because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. While more recently published health assessments of non-cancer endpoints were available, including the EPA OW Health Advisory {U.S. EPA, 1993c, 10492400}, HC GDWQ {HC, 2013b, 3603664}, WHO GDWQ {WHO, 2016b, 3859520}, ATSDR Toxicological Profile {ATSDR, 2017a, 3980254}, and CalEPA PHG {CalEPA, 2018c, 10489861}, these health assessments did not introduce new science (e.g., the toxicity value was not based on a newer critical study) or use updated methodologies (e.g., BMD modeling for POD derivation) compared to the 1991 EPA IRIS Chemical Assessment {U.S. EPA, 1991b, 10293342}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

Nitrate toxicity is due primarily to its conversion to nitrite, which oxidizes the $Fe^{(+2)}$ form of iron in hemoglobin to the $Fe^{(+3)}$ state. The resulting compound, methemoglobin, does not bind oxygen, resulting in reduced oxygen transport in blood from lungs to tissues. This is of particular concern in infants, especially between the ages of 0–3 months, as their gastrointestinal tracts have a high pH favoring the growth of nitrate-reducing bacteria {U.S. EPA, 1991b, 10293342}. Therefore, in this health assessment, EPA selected two studies that evaluated cases of methemoglobinemia in infants in the United States {Bosch, 1950, 3841331; Walton, 1951, 3002705} as the critical studies {U.S. EPA, 1991b, 10293342}.

Bosch et al. (1950, 3841331) evaluated 139 cases of methemoglobinemia-induced cyanosis, with cases ranging in age from 8 days up to 5 months. Reportedly, 90% of cases of cyanosis occurred in infants less than 2 months. Sampling data of nitrate concentrations in well water supplied to the children identified that none of the wells contained < 10 mg/L of nitrate-nitrogen; most sampled wells contained elevated levels of nitrate-nitrogen. Sampling also revealed high levels of coliform bacterial contamination in the well water. Walton et al. (1951, 3841331) presented the results of an American Public Health Association survey on infant methemoglobinemia morbidity and mortality, resulting from the ingestion of nitrate-contaminated well water across all 50 U.S. states. The survey results showed that no cases of methemoglobinemia occurred in infants consuming water containing < 10 mg/L nitrate-nitrogen, and five cases occurred in infants exposed to water containing 11–20 mg/L; most of the clinical cases of infantile methemoglobinemia that were reported were associated with levels of nitrate-nitrogen in the water > 20 mg/L. Therefore, based on the findings of these two studies, a NOAEL of 10 mg/L was selected as the POD for derivation of the oral reference dose. Nitrate is normally expressed as the amount of nitrogen within the nitrate molecule commonly shown as mg nitrate-nitrogen/L (1 mg nitrate-nitrogen = 4.4 mg nitrate). The NOAEL was then converted to 1.6 mg nitrate-nitrogen/kg/day, considering the ingestion of drinking water used to prepare infant's formula as 0.64 L/day for a 4 kg infant (0.16 L/kg/day) {Davidson, 1975, 10634783}. A total uncertainty factor of 1 was then applied to this POD due to availability of data to define the NOAEL for the critical toxic effect in the most sensitive human subpopulation. The oral RfD was calculated to be 1.6 mg/kg/day for nitrate {U.S. EPA, 1991b, 10293342}.

Most studies of nitrate ingestion by humans or animals have yielded negative or equivocal evidence of carcinogenicity. EPA has yet to perform any quantitative cancer risk calculations for nitrate {U.S. EPA, 1990a, 10492389; U.S. EPA, 1991b, 10293342}.

6.1.27.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the CalEPA PHG {CalEPA, 2018b, 10489857} was used to assign the date limit {CalEPA, 2018c, 10489861}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for nitrate was defined as one year prior to July 2017 resulting in a search date range from July 1, 2016 to March 1, 2022.

From this literature search, 9,265 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Seven-hundred and eighty-nine of these 9,265 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 8,476 of the 9,265 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-82.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for nitrate and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388 }).

Table 6-82. Evidence Stream Heat Map Results for Nitrate[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,775
Environmental Fate	–	4,959
Human	All	2,824
	Epidemiologic Quantitative Analyses	91
In Vitro	–	2,054
No Tag	–	636
Total Unique Studies		**8,476**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.27.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-83 shows the comparison of the basis for the existing and potential MCLGs for nitrate.

Table 6-83. Comparison of the Basis for the Existing and Potential MCLGs for Nitrate

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990a, 10492389)	–	–	–	–[d]	–	–	–	–	–	–
EPA (1990a, 10492389)	Bosch et al. (1950, 3841331); Walton (1951, 3002705)	Methemoglobinemia in infants	–	–	1.6 as nitrate-nitrogen	100%	Infants	4 kg infant, 0.64 L/day	10	–
Relevant Health Assessment Identified in SYR 4										
EPA (1990a, 10492389)	–	–	–[e]	–[d]	–	–	–	–	–	–
EPA (1991b, 10293342)	Bosch et al. (1950, 3841331); Walton (1951, 3002705)	Methemoglobinemia in infants	–	–	1.6 as nitrate-nitrogen	100%[f]	Infants (birth to < 1 year)	143 mL/kg/day	–	10

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] EPA did not assign a cancer descriptor to nitrate.
[e] EPA has yet to perform any quantitative cancer risk calculations for nitrate {U.S. EPA, 1990a, 10492389; U.S. EPA, 1991b, 10293342}.
[f] For EPA assessments completed prior to 2000, EPA applied an RSC of 100% when the adverse effect was related to exposure in children because the source of exposure for the critical study was drinking water {U.S. EPA, 2016c, 6557097}. In SYR 3, EPA maintained an RSC of 100%. In SYR 4, no new assessments were introduced that introduced new science since SYR 3 (i.e., newer assessments are based on the same critical study as the OW Criteria Document {U.S. EPA, 1991b, 10293342}; therefore, EPA maintained an RSC of 100% for SYR 4.

6.1.27.5 SYR 4 Health Effects Conclusion

The existing NPDWR for nitrate was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 1.6 mg/kg/day for nitrate {U.S. EPA, 1990a, 10492389}, DWI and BW values for infants (i.e., 4 kg and 0.64 L/day), and an RSC of 100%, the MCLG was set at 10 mg/L {U.S. EPA, 1991a, 5499}. Based on the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1991 EPA IRIS Chemical Assessment to derive the potential MCLG {U.S. EPA, 1991b, 10293342} because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Based on an RfD of 1.6 mg/kg/day {U.S. EPA, 1991b, 10293342}, an adjusted DWI-BW ratio of 143 mL/kg bw/day for infants, birth to < 1 year (see Section 4.2 for further information on target population selection), and an RSC of 100% {U.S. EPA, 2016c, 6557097}, EPA calculated a potential MCLG of 10 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 10 mg/L.

6.1.28 Nitrite (as N) (CAS# 14797-65-0 | DTXSID5024219)

6.1.28.1 Basis of the Existing MCLG

EPA published the current NPDWR for nitrite on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established both an MCLG and an MCL of 1 mg/L (as nitrogen (N)). EPA based the MCLG on extrapolation from nitrate, assuming the conversion of 10 percent of nitrate-nitrogen to nitrite-nitrogen {U.S. EPA, 1990a, 10492389). There is no cancer classification available for nitrite {U.S. EPA, 1990a, 10492389}.

6.1.28.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for nitrite that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-84.

Table 6-84. Assessments Identified for Nitrite

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1987y, 10284427}	0.1 (as nitrite-N)[d]	NOEL	Walton (1951, 3002705)	–	–	–
EPA OW Drinking Water Criteria {U.S. EPA, 1990a, 10492389}	**0.16 (as nitrite-N)[e]**	**NOAEL**	**Bosch et al., (1950, 3841331); Walton (1951, 3002705)**	–	–	–
EPA OW Health Advisory {U.S. EPA, 1993c, 10492400}	0.16 (as nitrite-N)	NOAEL	Bosch et al., (1950, 3841331); Walton (1951, 3002705)	–	–	–
HC GDWQ {HC, 2013b, 3603664}	–[f]	–	–	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2016b, 3859520}	–[g]	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2017a, 3980254}	0.1 (as nitrite) 0.03 (as nitrite-N)[h]	NOAEL	Walton (1951, 3002705)	–	–	–
CalEPA PHG {CalEPA, 2018b, 10489857}	–[i]	–	–	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOEL = no-observed-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference values" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), tolerable daily intake (TDI), or acceptable daily dose (ADD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Nitrite is normally expressed as the as the amount of nitrogen within the nitrite molecule commonly shown as mg nitrite-nitrogen/L.

[e] EPA OW (1990a, 10492389) derived an RfD for nitrite for the human infant by multiplying the RfD for nitrate-N (1.6 mg/kg/day) by a conversion rate of 10% to account for the conversion of nitrate to nitrite in the gastrointestinal tract of infants.

[f] HC (2013b, 3603664) did not calculate an oral reference value but instead relied on a drinking water NOAEL of 45 mg/L as nitrate based on the weight of evidence from human studies to establish a drinking water health-based value (HBV) for nitrite (3 mg/L). The NOAEL was multiplied by a molar conversion factor and a factor of 0.1 to account for the estimated conversion rate of nitrate to nitrite in the gastrointestinal tract of infants.

[g] WHO (2016b, 3859520) did not calculate an oral reference value but instead relied on a drinking water NOAEL of 50 mg/L as nitrate based on the weight of evidence from human studies to establish a drinking water guideline value for nitrite (3 mg/L). The NOAEL was multiplied by a molar conversion factor and a factor of 0.1 to account for the estimated conversion rate of nitrate to nitrite in the gastrointestinal tract of infants.

[h] ATSDR (2017a, 3980254) derived an MRL of 0.1 mg/kg/day as nitrite that was converted by EPA to 0.03 mg/kg/day as nitrite-N using a conversion factor (1 mg nitrite = 0.304 mg nitrite-N).

[i] CalEPA (2018b, 10489857) did not derive an ADD specifically for nitrite, but derived an ADD of 13.2 mg/kg/day for nitrate based on a drinking water NOAEL of 45 mg/L {Bosch et al., 1950, 3841331; Walton, 1951, 3002705; Sadeq et al., 2008, 867021} and subsequently, a PHG for nitrate of 45 mg/L. To establish the drinking water PHG for nitrite (3.3 mg/L), CalEPA multiplied the PHG for nitrate by a molar conversion factor and a factor of 0.1 to account for the estimated conversion rate of nitrate to nitrite in the gastrointestinal tract of infants.

The health assessment selected for SYR 4 is the EPA OW Drinking Water Criteria Document {U.S. EPA, 1990a, 10492389} because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. While more recently published health assessments of non-cancer endpoints were available, including EPA OW Health Advisory {U.S. EPA, 1993c, 10492400}, HC GDWQ {HC, 2013b, 3603664}, WHO GDWQ {WHO, 2016b, 3859520}, ATSDR Toxicological Profile {ATSDR, 2017a, 3980254}, and CalEPA PHG {CalEPA, 2018c, 10489861}, these health assessments did not introduce new science (e.g., the toxicity value was not based on a newer critical study) or use updated methodologies (e.g., BMD modeling for POD derivation) compared to the older EPA health assessment {U.S. EPA, 1990a, 10492389}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals).

Few human studies exist on the toxicity of direct nitrite exposure. Nitrate is reduced to nitrite by oral and gastrointestinal bacteria. Nitrite then oxidizes the $Fe^{(+2)}$ form of iron in hemoglobin to the $Fe^{(+3)}$ state forming methemoglobin, which does not bind oxygen and results in reduced oxygen transport in blood

from lungs to tissues {U.S. EPA, 1990a, 10492389}. After examining the available animal toxicological studies, EPA found that animals are not as sensitive to the effects of nitrite as human infants (via nitrate exposure) and determined that the available animal data "suggest that a dose of up to about 10 mg N/kg/day does not cause any adverse effects" (i.e., NOAEL of 10 mg N/kg/day) {U.S. EPA, 1990a, 10492389}. Infants, especially between the ages of 0–3 months, are most susceptible as their gastrointestinal tracts have a high pH favoring the growth of nitrate reducing bacteria. The NOAEL of 10 mg N/kg/day based on animal toxicology studies is much higher than the 1.6 mg N/kg/day found to cause methemoglobinemia in infants. Therefore, EPA decided to use data from nitrate exposure in infants, rather than from nitrite exposure in animals, to derive the human oral RfD for nitrite {U.S. EPA, 1990a, 10492389}.

For the derivation of the nitrate RfD, EPA selected two studies that evaluated cases of methemoglobinemia in infants in the United States as the critical studies {Bosch, 1950, 3841331; Walton, 1951, 3002705}. Both studies found that no cases of methemoglobinemia at exposures < 10 mg/L (1.6 mg nitrate-nitrogen/kg/day), and higher numbers of cases were identified at the higher exposures. Using these data from these two studies, a NOAEL of 10 mg/L (1.6 mg nitrate-nitrogen/kg/day) was selected as the POD for derivation of the oral reference dose {Bosch, 1950, 3841331; Walton, 1951, 3002705}. A total uncertainty factor of 1 was then applied to this POD due to availability of data to define the NOAEL for the critical toxic effect in the most sensitive human subpopulation. The NOAEL for nitrite in humans was estimated from the NOAEL for nitrate with a 10% conversion factor (a conservative factor to account for bacterial reduction) assumed in infants, the most susceptible subpopulation. After applying the total UF and accounting for the 10% conversion factor, the oral RfD was calculated to be 0.16 mg/kg/day for nitrite {U.S. EPA, 1990a, 10492389}.

Most studies of nitrite ingestion by humans or animals have yielded negative or equivocal evidence of carcinogenicity. EPA has not performed quantitative cancer risk calculations for nitrite {U.S. EPA, 1987y, 10284427; U.S. EPA, 1990a, 10492389}.

6.1.28.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the CalEPA PHG was used to assign the date limit {CalEPA, 2018c, 10489861}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for nitrite was defined as one year prior to July 2017 resulting in a search date range from July 1, 2016 to February 3, 2022.

From this literature search, 4,248 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two-hundred and twenty-eight of these 4,248 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 4,020 of the 4,248 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-85.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for nitrite and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-85. Evidence Stream Heat Map Results for Nitrite[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,698
Environmental Fate	–	1,657
Human	All	1,388
	Epidemiologic Quantitative Analyses	27
In Vitro	–	1,437
No Tag	–	198
Total Unique Studies		**4,020**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.28.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-86 shows the comparison of the basis for the existing and potential MCLGs for nitrite.

Table 6-86. Comparison of the Basis for the Existing and Potential MCLGs for Nitrite

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990a, 10492389)	–	–	–	–[d]	–	–	–	–	–	–
EPA (1990a, 10492389)	Bosch et al., (1950, 3841331); Walton (1951, 3002705)	Methemoglobinemia in infants	–	–	0.16 as nitrite-nitrogen	100%	Infants	4 kg infant, 0.64 L/day	1	–
Relevant Health Assessment Identified in SYR 4										
EPA (1990a, 10492389)	–	–	–[e]	–[d]	–	–		–	–	–
EPA (1990a, 10492389)	Bosch et al., (1950, 3841331); Walton (1951, 3002705)	Methemoglobinemia in infants	–	–	0.16 as nitrite-nitrogen	100%[f]	Infants (birth to < 1 year)	143 mL/kg/day	–	1

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] EPA did not assign a cancer descriptor to nitrite. Most studies of nitrite ingestion by humans or animals have yielded negative or equivocal evidence of carcinogenicity.

[e] EPA has not performed quantitative cancer risk calculations for nitrite {U.S. EPA, 1987y, 10284427; U.S. EPA, 1990a, 10492389}.

[f] For EPA assessments completed prior to 2000, EPA applied an RSC of 100% when the adverse effect was related to exposure in children because the source of exposure for the critical study was drinking water {U.S. EPA, 2016c, 6557097}. In SYR 3, EPA maintained an RSC of 100%. In SYR 4, no new assessments were introduced that introduced new science since SYR 3 (i.e., newer assessments are based on the same critical study as the OW Criteria Document {U.S. EPA, 1991b, 10293342}); therefore, EPA maintained an RSC of 100% for SYR 4.

6.1.28.5 SYR 4 Health Effects Conclusion

The existing NPDWR for nitrite was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.16 mg/kg/day, DWI and BW values for infants (i.e., 0.64 L/day and 4 kg), and an RSC of 100%, the MCLG was set at 1 mg/L {U.S. EPA, 1990a, 10492389; U.S. EPA, 1991a, 5499). At the time, a cancer descriptor was not available {U.S. EPA, 1990a, 10492389}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1990 EPA OW Drinking Water Criteria Document {U.S. EPA, 1990a, 10492389} to derive the potential MCLG because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk (see Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals). Based on an RfD of 0.16 mg/kg/day, an adjusted DWI-BW ratio of 143 mL/kg bw/day for infants birth to < 1 year (see Section 4.2 for further information on target population selection), and an RSC of 100% {U.S. EPA, 2016c, 6557097}, EPA calculated a potential MCLG of 1 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 1 mg/L.

6.1.29 Pentachlorophenol (CAS# 87-86-5 | DTXSID7021106)

6.1.29.1 Basis of the Existing MCLG

EPA published the current NPDWR for pentachlorophenol on July 1, 1991, establishing an MCLG of 0 and an MCL of 0.001 mg/L {U.S. EPA, 1991j, 10492394}. EPA based the MCLG on a cancer classification of B2 {U.S. EPA, 1987z, 63692}, "probable human carcinogen," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The B2 classification was based on inadequate human data and sufficient evidence of carcinogenicity in animals {U.S. EPA, 1987z, 63692} (see Table 3-1 for more information on cancer classification). The MCL of 0.001 mg/L was based on analytical feasibility {U.S. EPA, 1991j, 10492394}.

6.1.29.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for pentachlorophenol that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-87.

Table 6-87. Assessments Identified for Pentachlorophenol

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	0.03	NOAEL	Schwetz et al. (1978, 63714)	–	–	D[d]
HC GDWQ {HC, 1987, 10524696}[e]	0.006	NOAEL	Schwetz et al. (1978, 63714)	–	–	–[f]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987z, 63692}	0.03	NOAEL	Schwetz et al. (1978, 63714)	0.12	NTP (1989, 6571197)	B2[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile and Addendum {ATSDR, 2001a, 3004804; 2012d, 6567151}	0.001	LOAEL	Beard and Rawlings (1998, 1414258)	–	–	–
WHO GDWQ {WHO, 2003g, 10509432}	–[g]	–	–	–	–	–[g]
EPA OPP RED (2008b, 1593840)	0.005	LOAEL	Mecler (1996, 6546813)	0.07	NTP (1989, 6571197)	B2
CalEPA PHG {CalEPA, 2009a, 10489851}	0.001	LOAEL	Beard and Rawlings (1998, 1414258; 1999, 1415083)	0.0834, 0.0811[h]	NTP (1989, 6571197)	NA[i]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010g, 6547087}	0.005	LOAEL	Mecler (1996, 6546813)	**0.4**	**NTP (1989, 6571197)**	**L[j]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), acceptable daily dose (ADD), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] The Guidelines for Canadian Drinking Water Quality Summary Table lists the date of assessment for pentachlorophenol as 1987 (reaffirmed in 2005). The guideline technical document for chlorophenols is dated 1987.

[f] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment but states that, regarding its potential carcinogenicity, pentachlorophenol is "included in Group VA (inadequate data for evaluation)" {HC, 1987, 10524696}.

[g] WHO did not derive an oral RfV for pentachlorophenol. In addition, the health assessment states that there is conclusive evidence of carcinogenicity of pentachlorophenol (PCP) in one animal species, and "it was therefore considered prudent to treat PCP as a potential carcinogen."

[h] CalEPA derived a human cancer potency value of 0.0834 $(mg/kg/day)^{-1}$ using the linearized multistage model and a cancer slope factor of 0.0811 $(mg/kg/day)^{-1}$ using the LED_{10} model. The resulting public health-protective drinking water concentrations for pentachlorophenol were comparable using the two different models.

[i] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment but states that "there is suggestive but inadequate epidemiological evidence that exposure to PCP is related to some human cancers."

[j] Based on EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2010 EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010g, 6547087} (bolded in Table 6-87) because this is the most recently published EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for pentachlorophenol. Refer to Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the selected 2010 EPA IRIS health assessment, a 2-year feed study in B6C3F1 mice was chosen as the critical study to derive an oral CSF {NTP, 1989, 6571197}. In this study, male and female B6C3F1 mice

(50/sex/dose) were exposed to two technical grades of PCP in feed containing 0, 100, or 200 ppm of technical-grade (tPCP) or 0, 100, 200, or 600 ppm of a pesticidal formulation of PCP (Dowicide EC-7, EC-7) for 2 years. The study reported dose-related increases in the incidence of hepatocellular adenomas and carcinomas, and adrenal gland pheochromocytomas in both sexes. Increased incidence of hemangioma and hemangiosarcoma were also observed in exposed female mice. The combined risk estimates for liver, adrenal gland, and circulatory system tumors observed in male and female mice exposed to tPCP were selected as the POD. The 95% upper bound human-equivalent combined risk for male and female mice exposed to tPCP were 0.4 and 0.083 mg/kg/day, respectively. A multistage model using linear extrapolation from the POD was performed to derive an oral slope factor. Risk estimates for tPCP were higher than those for EC-7; thus, the values for male and female mice exposed to tPCP were used to determine the oral slope factor of 0.4 $(mg/kg/day)^{-1}$ for PCP.

In the 2010 EPA IRIS assessment, EPA determined that pentachlorophenol is "likely to be carcinogenic in humans" {U.S. EPA, 2010g, 6547087}, which corresponds to a cancer classification of L, based on evidence demonstrating carcinogenicity in animals as well as supporting evidence from epidemiology studies following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. Because pentachlorophenol is classified as "likely to be carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.29.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for pentachlorophenol was defined as one year prior to December 2015 resulting in a search date range from December 1, 2014 to March 1, 2022.

From this literature search, 1,793 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Fifty-six of these 1,793 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,737 of the 1,793 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-88.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for pentachlorophenol and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388 }).

Table 6-88. Evidence Stream Heat Map Results for Pentachlorophenol[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	598
Environmental Fate	–	540
Human	All	1,040
	Epidemiologic Quantitative Analyses	104
In Vitro	–	548
No Tag	–	66
Total Unique Studies		**1,737**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.29.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-89 shows the comparison of the basis for the existing and potential MCLGs for pentachlorophenol.

Table 6-89. Comparison of the basis for the Existing and Potential MCLGs for Pentachlorophenol

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987z, 63692)	NTP (1989, 6571197)	Pooled incidence of hepatocellular adenomas and carcinomas, pheochromocytomas, malignant pheochromocytomas, and hemangiosarcomas and hemangiomas in female B6C3F1 mice	0.12	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2010g, 6547087)	NTP (1989, 6571197)	Hepatocellular adenomas or carcinomas and adrenal benign or malignant pheochromocytomas	0.4	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.29.5 SYR 4 Health Effects Conclusion

The existing NPDWR for pentachlorophenol was published on July 1, 1991 {U.S. EPA, 1991j, 10492394}. Based on a cancer classification of B2 {U.S. EPA, 1987z, 63692}, "probable human carcinogen," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010g, 6547087} because this is the most recently published EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for pentachlorophenol. In the 2010 EPA IRIS health assessment, the CSF was set at 0.4 $(mg/kg/day)^{-1}$ and the cancer classification was updated to L, "likely to be carcinogenic to humans," according to EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For pentachlorophenol, more recent information does not support a change to the MCLG.

6.1.30 Selenium (CAS# 7782-49-2 | DTXSID9021261)

6.1.30.1 Basis of the Existing MCLG

EPA published the current NPDWR for selenium on January 30, 1991, establishing both an MCLG and MCL of 0.05 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a maximum safe intake of 0.4 mg/person/day and a cancer classification of D {U.S. EPA, 1990e, 10509467}, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991a, 5499} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). There is no RfD for selenium in the 1991 NPDWR FR due to selenium's status as a nutrient {U.S. EPA, 1991a, 5499}. The 0.4 mg/day safe level was based on data {Yang et al.,1989a, 86906; 1989b, 86907} that extrapolated from blood selenium levels to estimate dietary intake in the studied population {U.S. EPA, 1991a, 5499}. As described in the January 30, 1991 {U.S. EPA, 1991a, 5499}, the agency considered selenium's status as a nutrient (based on a maximum safe intake level of 0.4 mg/day {U.S. EPA, 1990e, 10509467}) and did not use the typical procedure for deriving the MCLG.

6.1.30.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for selenium that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-90.

Table 6-90. Assessments Identified for Selenium

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990e, 10509467}	0.003	LOAEL	Yang et al. (1983, 69903)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991k, 10293324}	0.005	NOAEL	Yang et al. (1989b, 86907)	–	–	D[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
NAS/IOM (2000, 786229)	0.4 mg/day[e]	–[e]	Yang and Zhou[e] (1994, 75883)	–	–	–
ATSDR Toxicological Profile (2003a, 2990677)	**0.005**	**NOAEL**	**Yang and Zhou (1994, 75883)**	–	–	-
CalEPA PHG (2010f, 10489853)	Refer to IRIS[f]	Refer to IRIS[f]	Refer to IRIS[f]	–	–	Refer to IRIS[g]
WHO GDWQ (2003i, 10509459)	–	–	–	–	–	–
HC GDWQ (2014a, 10528913)	–	–	–	–	–	Refer to IRIS[g]

Notes: POD = point of departure; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The IRIS Chemical Assessment Summary reports a cancer descriptor of D, "not classifiable as to human carcinogenicity," for selenium, sodium selenate, sodium selenite, selenious acid, selenic acid, and sodium selenide based on inadequate human data and inadequate evidence of carcinogenicity in animals. It also reports that evidence for selenium sulfide is sufficient for a B2, "probable human carcinogen," classification.

[e] This health assessment reports that the TDI upper level (UL) of 400 µg/day developed by the Institute of Medicine {2000, 786229} was used to calculate a health-based value (HBV) for selenium in drinking water. The UL of the TDI is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. It was derived from a NOAEL of 800 µg/day established by Yang and co-workers {Yang et al., 1989b, 86907, 86906; Yang and Zhou, 1994, 75883} using a UF of 2× to protect sensitive individuals.

[f] The CalEPA PHG assessment used the RfD reported in the IRIS Chemical Assessment Summary to calculate a total daily oral intake of 0.35 mg/day for selenium by multiplying the RfD by the default adult male body weight of 70 kg.

[g] This health assessment cites the cancer classifications of D for selenium and B2 for selenium sulfide reported in the IRIS Chemical Assessment Summary per EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

The health assessment selected for SYR 4 is the 2003 ATSDR Toxicological Profile {ATSDR, 2003a, 2990677} (bolded in Table 6-90) because it derives an oral toxicity value, used the best available science in its evaluation of non-cancer risk, and its toxicity value is based on a more recent critical study than that of the 1991 EPA IRIS Chemical Assessment Summary for selenium {U.S. EPA, 1991k, 10293324}. Although more recent health assessments were available, the 2003 CalEPA PHG {CalEPA, 2010f, 10489853} referenced the oral toxicity value derived in the older EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991k, 10293324}, the WHO GDWQ {WHO, 2003i, 10509459} and the HC GDWQ {HC, 2014a, 10528913}, these more recent health assessments did not derive oral toxicity values for selenium. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the selected 2003 ATSDR health assessment, a dietary study by Yang and Zhou (1994, 75883) comparing the incidence of clinical symptoms of selenosis at selenium and selenium levels in blood was selected as the critical study to derive a chronic MRL. A NOAEL of 0.015 mg/kg/day was established based on blood levels of selenium in five individuals who resided in a high-selenium site and who recovered from dermal effects of selenium toxicity (i.e., nail sloughing) {Yang and Zhou, 1994, 75883}.

An uncertainty factor of 3× for intraspecies variability was then applied to this POD. After applying this uncertainty factor, the MRL was calculated to be of 0.005 mg/kg/day.

The 2003 ATSDR Toxicological Profile does not assign a cancer descriptor for selenium, however, the EPA IRIS Chemical Assessment categorized selenium as Group D, "not classifiable as to human carcinogenicity," due to inadequate human and animal evidence {U.S. EPA, 1991k, 10293324} based on the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.30.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for selenium was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to February 4, 2022.

From this literature search, 5,756 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two hundred and thirty-seven of these 5,756 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 5,519 of the 5,576 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-91.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for selenium and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-91. Evidence Stream Heat Map Results for Selenium[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	2,842
Environmental Fate	–	1,166
Human	All	3,141
	Epidemiologic Quantitative Analyses	136
In Vitro	–	2,705
No Tag	–	211
Total Unique Studies		**5,519**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tags.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.30.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-92 shows the comparison of the basis for the existing and potential MCLGs for selenium.

Table 6-92. Comparison of the Basis for the Existing and Potential MCLGs for Selenium

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1991a, 5499)	–	–	–	D	–	–	–	–	–	–
EPA (1990e, 10509467)	Yang et al. (1983, 69903)	Absence of clinical selenosis (hair or fingernail loss; numbness in fingers or toes; circulatory problems)	–	–	0.21 mg/day[d]	50%	General Population	70 kg adult, 2 L/day	0.05[e]	–
Relevant Health Assessment Identified in SYR 4										
EPA (1991k, 10293324)	–	–	–	D	–	–	–	–	–	–
ATSDR (2003a, 2990677)	Yang and Zhou (1994, 75883)	Absence of clinical selenosis (hair or fingernail loss; numbness in fingers or toes; circulatory problems)	–	–	0.005	20%[f]	General Population	33.8 mL/kg/day	–	0.03

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values are expressed in mg/kg/day unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] As described in the January 30, 1991 FR {U.S. EPA, 1991a, 5499}, EPA partially considered selenium's status as a nutrient and did not use the typical procedure for deriving the MCLG. Hence, there is no specific reference to an RfD for selenium in the 1991 FR. The 1991 FR did, however, designate 3.2 mg/day as the POD and a total UF of 15 (accounting for human variability and the use of a LOAEL). The RfV is calculated by dividing the POD by the total uncertainty factors. Thus 3.2 mg/day ÷ 15 = 0.21 mg/day.
[e] (0.21 mg/day × 0.5 RSC) ÷ 2 L/day = 0.05 mg/L MCLG.
[f] Selection of 20% RSC in SYR 3 is described in a footnote of Table 33b in the EPA SYR 3 Summary Report (2016c, 6557097).

6.1.30.5 SYR 4 Health Effects Conclusion

The existing NPDWR for selenium was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a maximum safe intake level of 0.4 mg/day {U.S. EPA, 1990e, 10509467}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg) and an RSC of 50%, EPA set the MCLG at 0.05 mg/L and assigned selenium a cancer classification of D {U.S. EPA, 1990e, 10509467}, "not classifiable as to human carcinogenicity," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. There is no RfD for selenium in the 1991 NPDWR FR based on selenium's status as a nutrient {U.S. EPA, 1991a, 5499}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the ATSDR Toxicological Profile {ATSDR, 2003a, 2990677} to derive the potential MCLG because it derives an oral toxicity value, used the best available science in its evaluation of non-cancer risk, and its toxicity value is based on a more recent critical study than the EPA IRIS Chemical assessment for selenium. Based on an RfD of 0.005 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20% {U.S. EPA, 2016, 6557097}, EPA calculated a potential MCLG of 0.034 mg/L {U.S. EPA, 1991a, 5499}. Based on the analysis and conclusion presented in EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991k, 10293324} health assessment, the cancer classification was maintained as D, "not classifiable as to human carcinogenicity," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.05 mg/L to the potential MCLG of 0.034 mg/L.

6.1.31 2,4,5-Trichlorophenoxypropionic acid (2,4,5-TP; Silvex) (CAS# 93-72-1 | DTXSID0021387)

6.1.31.1 Basis of the Existing MCLG

EPA published the current NPDWR for 2,4,5-TP on January 30, 1991, establishing both an MCLG and an MCL of 0.05 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a noncancer reference dose of 0.008 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1987aa, 10532205}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.31.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for 2,4,5-TP that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-93.

Table 6-93. Assessments Identified for 2,4,5-TP (Silvex)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987aa, 10532205}	0.008	NOAEL	Mullison (1966, 10270860)	–	–	D[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}[e]	0.0075	NOAEL	Mullison (1966, 10270860)	–	–	D[d]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988e, 10270857}	**0.008**	**NOEL**	**Mullison (1966, 10270860); Gehring and Betso (1978, 6670196)[f]**	–	–	D[d]
CalEPA PHG {CalEPA, 2014, 10489858}	0.0003	NOAEL	Mullison (1966, 10270860)	–	–	–
WHO GDWQ {WHO, 2003j, 10509427}	0.003[g]	NOAEL	Mullison (1966, 10270860)[g]	–	–	–[h]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; NOEL = no-observed-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily dose (ADD), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] The information for the OW Health Advisory is extracted from a book chapter, Reviews of Environmental Contamination and Toxicology, Volume 104, 1988 by Springer-Verlag New York Inc. The OW Health Advisory recorded in the book chapter is copied from information in the draft EPA Health Advisory for Silvex document {U.S. EPA, 1987bb, 10510385}.

[f] EPA assumed that Mullison (1966, 10270860) and Gehring and Betso (1978, 6670196) reported on the same study based on identical dose levels and similar experimental details and results descriptions, and on the fact that Gehring and Betso (1978, 6670196) cites Mullison (1966, 10270860) as a published source of the data.

[g] This TDI established by WHO (2003j, 10509427) was based on a two-year study of toxicity and carcinogenicity in dogs. WHO cites Mullison (1966, 10270860) as the critical study.

[h] This health assessment does not report a cancer descriptor, but states that "Chlorophenoxy herbicides, as a group, have been classified in Group 2B (possibly carcinogenic to humans) by IARC. However, the available data from studies in exposed populations and experimental animals do not permit assessment of the carcinogenic potential to humans of any specific chlorophenoxy herbicide."

The health assessment selected for SYR 4 is the 1988 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988e, 10270857} (bolded in Table 6-93) because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Although more recent health assessments of non-cancer endpoints were available, including the CalEPA PHG {CalEPA, 2014, 10489858} and WHO GDWQ {WHO, 2003j, 10509427}, they were based on the same critical study {Mullison 1966, 10270860} as the 1988 EPA IRIS Chemical Assessment Summary (see Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals). In the selected health assessment, EPA chose a two-year oral bioassay {Mullison, 1966, 10270860; Gehring and Betso, 1978, 6670196} to derive a POD for the chronic oral RfD. In this bioassay, groups of four male and four female beagle dogs were fed diets containing the herbicide KUROSAL® SL, the potassium salt of Silvex, at calculated doses of 0, 0.75, 2.5, or 7.4 mg/kg/day after adjustments for the diet formulation containing the potassium salt. A NOEL of 0.75 mg/kg/day based on the critical effect of histopathological changes in livers of male and female dogs was used as the POD. A total uncertainty factor (UF) of 100 was applied: 10 for interspecies

variability and 10 for intraspecies variability. After applying the total UF, the oral RfD was calculated to be 0.008 mg/kg/day.

EPA concluded that the database for 2,4,5-TP (Silvex) is "insufficient to assess the carcinogenicity" {U.S. EPA, 1988e, 10270857} and categorized 2,4,5-TP (Silvex) as Group D, "not classifiable as to human carcinogenicity," according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.1.31.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for Silvex was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 7, 2022.

From this literature search, 13 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Following SWIFT-Review, all 13 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-94.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for silvex and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-94. Evidence Stream Heat Map Results for 2,4,5-TP (Silvex)[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	2
Environmental Fate	–	3
Human	All	9
	Epidemiologic Quantitative Analyses	2
In Vitro	–	3
No Tag	–	0
Total Unique Studies		**13**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.31.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-95 shows the comparison of the basis for the existing and potential MCLGs for 2,4,5-TP (Silvex).

Table 6-95. Comparison of the Basis for the Existing and Potential MCLGs for 2,4,5-TP (Silvex)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987aa, 10532205)	–	–	–	D	–	–	–	–	–	–
EPA (1987aa, 10532205)	Mullison (1966, 10270860); Gehring & Betso (1978, 6670196)	Histopathological changes in liver	–	–	0.008	20%	General Population	70 kg adult, 2 L/day	0.05	–
Relevant Health Assessment Identified in SYR 4										
EPA (1988e, 10270857)	–	–	–	D	–	–	–	–	–	–
EPA (1988e, 10270857)	Mullison (1966, 10270860); Gehring & Betso (1978, 6670196)	Histopathological changes in liver	–	–	0.008	20%	General Population	33.8 mL/kg/ day	–	0.05

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.31.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 2,4,5-TP (Silvex) was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.008 mg/kg/day {U.S. EPA, 1987aa, 10532205}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.05 mg/L and assigned 2,4,5-TP (Silvex) a cancer descriptor of D, "not classifiable as to human carcinogenicity," according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1988 EPA IRIS Chemical Assessment {U.S. EPA, 1988e, 10270857} to derive the potential MCLG because it is the most recent EPA health assessment that used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.008 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.05 mg/L. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 0.05 mg/L.

6.1.32 Styrene (CAS# 100-42-5 | DTXSID2021284)

6.1.32.1 Basis of the Existing MCLG

EPA published the current NPDWR for styrene on January 30, 1991, establishing both an MCLG and an MCL of 0.1 mg/L {U.S. EPA, 1991a, 5499}. The MCLG was based on a reference dose of 0.2 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1987cc, 10510381} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. A risk management safety factor of 10 was applied in the calculation of the MCLG to account for possible carcinogenicity {U.S. EPA, 1991a, 5499} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

The following table shows the final health assessments relevant to chronic toxicity available for styrene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-96.

Table 6-96. Assessments Identified for Styrene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987cc, 10510381}	0.2	NOAEL	Quast et al. (1978, 73657)	2.47	Ponomarkov and Tomatis (1978, 73514)	**C[d]**
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1987dd, 6574190}	0.2	NOAEL	Quast et al. (1979, 73641)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1991l, 5900}	0.2	NOAEL	Quast et al. (1979, 73641)	0.03	NCI (1979, 73493)	–[e]
WHO GDWQ {WHO, 2003k, 10509435}	0.0077	NOAEL	Litton Bionetics (1980, 10524451)	–	–	–
ATSDR Toxicological Profile; ATSDR Addendum {ATSDR, 2010a, 1937668; 2011, 10489750}	0.1[f]	LOAEL	Husain et al. (1985, 73581)	–	–	–
CalEPA PHG {CalEPA, 2010a, 10489854}	0.0016[g]	Oral BMD equivalent to the BMC_{05}	Cruzan et al. (2001, 51381)	**0.026[h]**	**Cruzan et al. (2001, 51381)**	**–[i]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level; BMD = benchmark dose; BMC_{05} = benchmark concentration corresponding to a 5% increase from control.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] This health assessment did not designate a cancer descriptor, but states that bioassays provide "sufficient animal evidence for the carcinogenic activity of styrene." {U.S. EPA, 1991l, 5900}

[f] This is an acute-duration oral MRL; ATSDR (2010a, 1937668) determined that the acute oral toxicity database provides suggestive evidence that neurotoxicity is the most sensitive target of styrene. An intermediate-duration oral MRL was not derived because the LOAELs identified in intermediate-duration studies were higher than the lowest LOAEL for neurotoxicity identified in the acute-duration critical study. A chronic-duration oral MRL was not derived because no long-term oral studies that examined neurological endpoints were identified.

[g] POD/UF was calculated by EPA based on a POD of 0.155 mg/kg/day from this health assessment (the equivalent oral dose to the BMC_{05} of 1.1 ppm from a two-year inhalation study in mice) and a total UF of 95.7. CalEPA (2010a, 10489854) determined that it is plausible that multiple effects on respiratory tissue associated with styrene inhalation may also occur with styrene ingestion and derived a health protective drinking water concentration based on noncancer effects of styrene; however, the final PHG derived by CalEPA was based on carcinogenic effects of styrene (lung tumors in mice).

[h] CalEPA (2010a, 10489854) derived several different cancer potency estimates for styrene using many different studies. The CSF reported here is the one used by CalEPA in the derivation of a PHG for styrene.

[i] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment but concludes that "there is sufficient evidence that styrene causes cancer in animals and limited evidence in humans."

The health assessment selected for SYR 4 is the CalEPA PHG {CalEPA, 2010a, 10489854} (bolded in Table 6-96) because it is the most recently published health assessment and used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for styrene. EPA also selected the EPA OW Drinking Water Criteria Document {U.S. EPA, 1987cc, 10510381} because this assessment designated a cancer descriptor. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals. In this health assessment, CalEPA selected a chronic inhalation mouse study {Cruzan, 2001, 51381} as the critical study. Male and female CD-1 mice (50/sex/exposure level) were exposed to

0, 20, 40, 80, or 160 ppm airborne styrene for 6 hours/day, 5 days/week for 104 weeks (males) or 97 weeks (females; terminated early because of low survival rates in the control group). Significant increases in the incidence of both lung bronchioalveolar adenomas and carcinomas were observed in both sexes at all tested concentrations. Dose-response analysis was performed using a linear multistage model on lung tumor data to derive a POD. The POD of 4.56 mg/kg/day was calculated after adjustments for a continuous exposure of 20 ppm in air to µg/L, $(\text{bodyweight})^{3/4}$ scaling, and assuming a breathing rate of 20,000 L/day and a 70 kg human body weight; additionally, the 80 ppm group was removed as an outlier and a time adjustment was applied to the female mouse data since they were terminated at 97 weeks. CalEPA then derived the cancer potency factor for male and for female mice, 0.026 $(\text{mg/kg/day})^{-1}$ for each sex respectively, from the lower 95% confidence limit on the POD.

The CalEPA PHG (2010a, 10489854) did not assign a cancer descriptor; however, EPA has categorized styrene as Group C, "possible human carcinogen" {U.S. EPA, 1987cc, 10510381}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, based on limited evidence of carcinogenicity in animals and the absence of human data. Because styrene is classified as a "possible human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.32.2 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for styrene was defined as one year prior to December 2015, resulting in a search range from December 1, 2014 to March 10, 2022. From the literature searches performed, a total of 3,096 unique studies were identified following review of the literature.

From this literature search, 3,096 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two-hundred and fifty-three of these 3,096 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 2,843 of the 3,096 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-97.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for styrene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-97. Evidence Stream Heat Map Results for Styrene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	859
Environmental Fate	–	504
Human	All	1,164
	Epidemiologic Quantitative Analyses	92
In Vitro	–	1,063
No Tag	–	497
Total Unique Studies		**2,843**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.32.3 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-98 shows the comparison of the basis for the existing and potential MCLGs for styrene.

Table 6-98. Comparison of the Basis for the Existing and Potential MCLGs for Styrene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987cc, 10510381)	Ponomarkov and Tomatis (1978, 73514)	Lung tumors	2.47	C	–	–	–	–	–	–
EPA (1987cc, 10510381)	Quast et al. (1979, 73641)	Reduced RBCs and iron deposits in the livers of dogs	–	–	0.2	20%	General Population	70 kg adult, 2 L/day	0.1[d]	–
Relevant Health Assessment Identified in SYR 4										
CalEPA (2010a, 10489854)	Cruzan, (2001, 51381)	Incidence of both lung bronchioalveolar adenomas and carcinomas in male and female mice	0.26	–[e]	–	–	–	–	–	–
EPA (1987cc, 10510381)	Ponomarkov and Tomatis (1978, 73514)	Lung tumors	–	C[f]	–	–	–	–	–	0

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable; RBCs = red blood cells.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity.

[e] CalEPA (2010, 10489854) concluded that there is sufficient evidence that styrene causes cancer in animals and there is limited evidence that it causes cancer in humans; however, no cancer descriptor was assigned.

[f] Because the 2010 CalEPA assessment did not designate a cancer descriptor, EPA maintained the cancer classification of C, "possible human carcinogen," assigned in the EPA OW Health Advisory {U.S. EPA, 1987cc, 10510381}

6.1.32.4 SYR 4 Health Effects Conclusion

The existing NPDWR for styrene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. The MCLG was based on an RfD of 0.2 mg/kg/day {U.S. EPA, 1987cc, 10510381} and a cancer classification of C, "possible human carcinogen" {U.S. EPA,1987cc, 10510381} according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Based on an RfD of 0.2 mg/kg/day {U.S. EPA, 1987cc, 10510381}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, and applying an additional risk management safety factor of 10 to account for possible carcinogenicity (see Table 3-1), EPA set the MCLG at 0.1 mg/L. EPA assigned styrene a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1987cc, 10510381}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the CalEPA PHG {CalEPA, 2010a, 10489854} because it is the most recently published health assessment and used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for styrene. Because the 2010 CalEPA assessment did not designate a cancer descriptor, EPA maintained the cancer classification of C, "possible human carcinogen" assigned in the EPA OW Health Advisory {U.S. EPA, 1987cc, 10510381}. However, based on **"**sufficient evidence that styrene causes cancer in animals and limited evidence in humans" presented in the 2010 CalEPA health assessment, EPA concluded that, there is potential to lower the current MCLG of 0.1 mg/L to the potential MCLG of zero.

6.1.33 Thallium (CAS# 7440-28-0 | DTXSID2036035)

6.1.33.1 Basis of the Existing MCLG

EPA published the current NPDWR for thallium on July 17, 1992, establishing an MCLG of 0.0005 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.00007 mg/kg/day {U.S. EPA, 1992d, 3994641} derived from a 13-week dietary study in rats {Stoltz et al., 1986, 10529404} and a cancer classification of D {U.S. EPA, 1992a, 3994641}, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992g, 10587719} based on the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). EPA set an MCL of 0.002 mg/L based on analytical feasibility {U.S. EPA, 1992g, 10587719}.

6.1.33.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for thallium that were published prior to the cut-off date of November 2020 for the qualifying health effects search. The health assessment selected for SYR 4 is bolded in Table 6-99.

Table 6-99. Assessments Identified for Thallium

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile {ATSDR, 1992b, 625991}	–[d]	–	–	–	–	–
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992d, 3994641}	**0.00007[e,f]**	**NOAEL**	**Stoltz et al. (1986, 10529404)/ Midwest Research Institute (1988, 626385)[g]**	–	–	–
EPA OW Health Advisory {U.S. EPA, 1992m, 626291}	0.00007[e,f]	NOAEL	Stoltz et al. (1986, 10529404)/ Midwest Research Institute (1988, 626385)[g]	–	–	–
CalEPA PHG {CalEPA, 1999c, 3987496}	0.00001[h]	NOAEL	Stoltz et al. (1986, 10529404)	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2009d, 626491}	–[i]	–	Midwest Research Institute (1988, 626385)	–	–	I[j]
EPA ORD PPRTV {U.S. EPA, 2010k, 1257667}	-[k]	NOAEL	Midwest Research Institute (1988, 626385)	–	–	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).
[c] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[d] The ATSDR Toxicological Profile states, "No data on effects of chronic-duration oral exposure to thallium were located. Therefore, acute-duration, intermediate-duration, and chronic-duration oral MRLs were not derived."
[e] This RfD for thallium is based on a 90-day drinking water study in rats exposed to thallium sulfate (Tl_2SO_4).
[f] The Drinking Water Criteria Document first derived an RfD of 0.08 µg Tl_2SO_4/kg/day and then applied a molecular weight conversion to derive a RfD of 0.07 µg Tl/kg/day.
[g] Midwest Research Institute (1988, 626385) is a revised final report of Stoltz et al. (1986, 10529404); both reports were prepared under EPA Project 8708-L18 {U.S. EPA, 2009d, 626491}.
[h] POD/UF was calculated by EPA based on a POD of 0.0405 mg Tl/kg/day (NOAEL from a 90-day drinking water study in rats exposed to Tl_2SO_4) and a total UF of 3,000.
[i] The IRIS Toxicological Review determined that an RfD could not be derived from the Midwest Research Institute (1988, 626385) study due to "critical limitations (e.g., high background incidence of alopecia, lack of histopathological examination of skin tissue in low- and mid-dose groups, and inadequate examination of objective measures of neurotoxicity)" {U.S. EPA, 2009d, 626491}.
[j] Based on EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.
[k] The EPA ORD PPRTV document reports that it is inappropriate to derive a chronic RfD for thallium for similar reasons cited in the IRIS Toxicological Review; however, a potential provisional RfD (p-RfD) value of 0.00001 mg/kg/day for thallium was included in an appendix to the PPRTV document. The appendix also included potential p-RfD values for salts of thallium (based on the potential p-RfD for thallium and calculated using molecular weight conversions).

The health assessment selected for SYR 4 is the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992d, 3994641} (bolded in Table 6-99) because it is an EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Although more recent health assessments of non-cancer endpoints for thallium were available, including CalEPA PHG {CalEPA, 1999c, 3987496}, IRIS Toxicological Review {U.S. EPA, 2009d, 626491}, and the EPA ORD PPRTV {U.S. EPA, 2010k, 1257667}, those health assessments did not introduce new science (i.e., they use the same critical study and same NOAEL as the 1992 EPA OW Drinking Water Criteria Document). See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals).

The 1992 EPA OW assessment selected a subchronic 90-day drinking water study in rats, Stoltz et al. (1986, 10529404), also published as Midwest Research Institute (MRI) {Midwest Research Institute, 1988, 626385}, as the critical study. In brief, Sprague-Dawley rats (20 rats/sex/dose) were dosed with thallium sulfate by daily oral gavage for 90 days at doses of 0.01, 0.05, or 0.25 mg/kg/day. The NOAEL for this study was determined to be 0.25 mg/kg/day of thallium sulfate (Tl_2SO_4), the highest dose tested, equivalent to 0.2 mg/kg/day of thallium (Tl), based on the lack of histopathological effects in the dosed rats. Other effects, however, were observed in all dosed groups including alopecia, coat changes (shedding of hair, rough coat), and changes in enzyme levels and serum electrolytes (e.g., increases in aspartate aminotransferase (SGOT/AST), LDH, and sodium levels; decreased glucose). Although the NOAEL is defined as 0.25 mg/kg/day thallium sulfate (Tl_2SO_4) based on the absence of histopathological effects, EPA noted some uncertainty concerning the endpoint evaluations in Stoltz et al. (1986, 10529404) {U.S. EPA, 1992d, 3994641}. A total UF of 3,000 was applied to the POD: 10 for interspecies variability, 10 for intraspecies variability, 10 for extrapolation from subchronic to chronic exposure, and 3 "to account for inadequate testing of other species, endpoints of toxicity, and uncertainties associated with the critical study" {U.S. EPA, 1992d, 3994641}. Because the critical study used to identify the NOAEL {Stoltz, 1986, 10529404} was conducted with thallium sulfate, the calculated RfD was adjusted to account for the molecular weight of thallium (Tl) vs. thallium sulfate (Tl_2SO_4). After applying the total UF and accounting for the molecular weight of thallium vs. thallium sulfate, the oral RfD was calculated to be 0.00007 mg/kg/day.

The 1992 EPA OW Drinking Water Criteria Document does not assign a cancer descriptor for thallium; however, the EPA IRIS Toxicological Review reported that there is "inadequate information to assess the carcinogenic potential" for thallium and thallium compounds {U.S. EPA, 2009d, 626491} according to

EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976} based on the lack of adequate animal and human studies.

6.1.33.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for thallium was defined as one year prior to December 2015, resulting in search date range from December 1, 2014 to February 22, 2022. From this literature search, 511 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty-three of these 511 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 488 of the 511 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-100.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for thallium and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-100. Evidence Stream Heat Map Results for Thallium[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	101
Environmental Fate	–	196
Human	All	294
	Epidemiologic Quantitative Analyses	28
In Vitro	–	108
No Tag	–	33
Total Unique Studies		**488**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.33.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-101 shows the comparison of the basis for the existing and potential MCLGs for thallium.

Table 6-101. Comparison of the Basis for the Existing and Potential MCLGs for Thallium

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992d, 3994641)	–	–	–	D	–	–	–	–	–	–
EPA (1992d, 3994641)	Stolz et al. (1986, 10529404)	Critical effect based on the absence of gross and light-microscopic histopathology in rats	–	–	0.00007	20%	General Population	70 kg adult; 2 L/day	0.0005	–
Relevant Health Assessment Identified in SYR 4										
EPA (2009d, 626491)	–	–	–	I	–	–	–	–	–	–
EPA (1992d, 3994641)	Stolz et al. (1986, 10529404)	Critical effect based on the absence of gross and light-microscopic histopathology in rats	–	–	0.00007	20%	General Population	33.8 mL/kg/ day	–	0.0004[d]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values are expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] Difference from Existing NPDWR MCLG based only on use of updated drinking water intake value {U.S. EPA, 2019, 7267482}.

6.1.33.5 SYR 4 Health Effects Conclusion

The existing NPDWR for thallium was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.00007 mg/kg/day {U.S. EPA, 1992d, 3994641}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.0005 mg/L and assigned thallium a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992g, 10587719}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1992 EPA OW Drinking Water Criteria Document {U.S. EPA, 1992d, 3994641} because although more recent health assessments exist, EPA did not identify new health information that would impact the existing MCLG. Based on an RfD of 0.00007 mg/kg/day {U.S. EPA, 1992d, 3994641}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.0004 mg/L. In the most recent health assessment of thallium's carcinogenic potential, the EPA IRIS Toxicological Review {U.S. EPA, 2009d, 626491}, the cancer classification for thallium was updated to I, "inadequate information to assess carcinogenic potential" for thallium and thallium compounds, according to EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that there is no health effects information available to support a change to the MCLG, however, there is a potential to lower the existing MCLG from 0.0005 mg/L to the potential MCLG of 0.0004 mg/L based on the updated exposure factor of 33.8 mL/kg/day for the general population (all ages) {U.S. EPA, 2019, 7267482}.

6.1.34 Toluene (CAS# 108-88-3 | DTXSID7021360)

6.1.34.1 Basis of the Existing MCLG

EPA published the current NPDWR for toluene on January 30, 1991 {U.S. EPA, 1991a, 5499}, establishing both an MCLG and an MCL of 1 mg/L. EPA based the MCLG on a reference dose of 0.2 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1990f, 713403}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.34.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity for toluene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-102.

Table 6-102. Assessments Identified for Toluene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990f, 713403}	0.2	$NOAEL_{ADJ}$	NTP (1990, 5934218)	–	–	D[d]
EPA OW Health Advisory {U.S. EPA, 1993e, 10492403}	0.2	$NOAEL_{ADJ}$	NTP (1990, 5934218)	–	–	D[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG {CalEPA, 1999d, 10489838}	0.022[e]	NOAEL	Hsieh et al. (1989, 61112)	–	–	–
WHO GDWQ {WHO, 2004j, 10509448}	0.223	$LOAEL_{ADJ}$	NTP (1990, 5934218)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2005f, 5176617}	0.08	$BMDL_{1SD}$	NTP (1990, 5934218)	–	–	I[f]
EPA ORD PPRTV {U.S. EPA, 2009e, 1257677}	Refer to IRIS	–	–	–	–	Refer to IRIS
HC GDWQ {HC, 2014a, 3049488}	**0.0097[g]**	**$NOAEL_{HED}$**	**Seeber et al. (2004, 9931353; 2005, 10510378)**	–	–	–[h]
ATSDR Toxicological Profile {ATSDR, 2017b, 10314675}	0.2[i]	NOAEL	Hsieh et al. (1989, 61112; 1990, 10480482; 1991, 74781)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; $NOAEL_{ADJ}$ = NOAEL adjusted for 5/7 days of exposure; $NOAEL_{HED}$ = human external dose equivalent to the NOAEL; dash (–) = not provided; $LOAEL_{ADJ}$ = the lowest-observed-adverse-effect level adjusted for 5/7 days of exposure; $BMDL_{1SD}$ = 95% lower confidence limit on the benchmark dose response corresponding to a change of one standard deviation from the control mean.

[a] Selected health assessment and chronic toxicity value are bolded.

[b] Oral reference values are expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors are expressed in $(mg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] This POD/UF was calculated by EPA based on a POD of 22 mg/kg/day (NOAEL from a subchronic study in mice) and a total UF of 1,000 reported in the CalEPA PHG.

[f] Based on EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[g] This TDI was derived using an inhalation NOAEL from human occupational studies. Using a physiologically-based pharmacokinetic (PBPK) model (based on Tardif et al. (1997, 83291)), an internal toluene blood concentration was estimated following inhalation exposure. Then, the estimated internal dose was used to determine an external oral dose from drinking water that would result in a similar blood concentration.

[h] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment but states that there is currently insufficient information from both animal and human studies to determine whether toluene is carcinogenic to humans.

[i] Intermediate-duration oral MRL; a chronic-duration oral MRL was not derived by ATSDR (2017b, 10314675) because there were no suitable chronic data for toluene.

The health assessment selected for SYR 4 is the 2014 HC GDWQ {HC, 2014a, 3049488} (bolded in Table 6-102) because it derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Although a more recent health assessment of non-cancer endpoints was available (the ATSDR Toxicological Profile (2017b, 10314675)), it did not introduce new science (e.g., the toxicity

value was not based on a newer critical study) compared to the HC GDWQ. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the HC GDWQ {HC, 2014a, 3049488}, two repeated-measure studies by Seeber et al. (2004, 9931353; 2005, 10510378) that evaluated the same population were chosen as the critical studies to derive a POD for the chronic RfD. In both studies, authors investigated the effects of toluene on cognitive function in a subsample of 192 subjects who participated in four examinations over the course of five years. There were no adverse effects for any of the endpoints assessed. A NOAEL of an external inhalation dose of 26 ppm was identified as the average of highly exposed individuals and was used as the POD. PBPK modeling was used to estimate the resultant internal toluene blood concentration of 0.0075 mg/L at the NOAEL (26 ppm) following inhalation exposure. PBPK modeling was further applied to estimate the oral human external dose ($NOAEL_{HED}$) of 0.097 mg/kg/day; the oral dose required to produce a similar blood concentration as would result from inhalation exposure. An uncertainty factor of 10 was applied for intraspecies variability. After applying this UF, the tolerable daily intake (TDI) was calculated to be 0.0097 mg/kg/day.

The 2014 HC GDWQ does not assign a cancer descriptor for toluene; however, EPA concluded that the evidence for toluene is "inadequate for an assessment of the carcinogenic potential" {U.S. EPA, 2005f, 5176617} according to EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

6.1.34.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the ATSDR Toxicological Profile was used to assign the date limit {ATSDR, 2017b, 10314675}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for toluene was defined as one year prior to June 2017 resulting in a search date range from June 1, 2016 to March 16, 2022.

From this literature search, 2,452 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One hundred and fifty of these 2,452 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 2,302 of the 2,452 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-103.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for toluene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-103. Evidence Stream Heat Map Results for Toluene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	460
Environmental Fate	–	857
Human	All	1,132
	Epidemiologic Quantitative Analyses	192
In Vitro	–	591
No Tag	–	284
Total Unique Studies		**2,302**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.34.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-104 shows the comparison of the basis for the existing and potential MCLGs for toluene.

Table 6-104. Comparison of the Basis for the Existing and Potential MCLGs for Toluene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990f, 713403)	–	–	–	D	–	–	–	–	–	–
EPA (1990f, 713403)	NTP (1989, 6571197)	Increased liver-to-brain weight ratio in male rats	–	–	0.2	20%	General Population	70 kg adult, 2 L/day	1	–
Relevant Health Assessments Identified in SYR 4										
EPA (2005f, 5176617)	–	–	–	I	–	–	–	–	–	–
HC (2014a, 3049488)	Seeber et al. (2004, 9931353; 2005, 10510378)	Absence of neurological health effects in human occupational exposure study	–	–	0.0097[d]	20%	General Population	33.8 mL/kg/day	–	0.06

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors are expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values are expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] This TDI was derived using an inhalation NOAEL from human occupational studies. Using a physiologically-based pharmacokinetic (PBPK) model, an internal toluene blood concentration was estimated following inhalation exposure. Then, the estimated internal dose was used to determine an external oral dose from drinking water that would result in a similar blood concentration.

6.1.34.5 SYR 4 Health Effects Conclusion

The existing NPDWR for toluene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.2 mg/kg/day {U.S. EPA, 1990f, 713403}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 1 mg/L and assigned toluene a cancer classification of D, "not classifiable as to human carcinogenicity," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2014 HC GDWQ {HC, 2014a, 3049488} to derive the potential MCLG because it derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.0097 mg/kg/day{HC, 2014a, 3049488}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.06 mg/L. Based on the analysis and conclusion presented in the EPA IRIS Chemical Assessment Summary {U.S. EPA, 2005f, 5176617}, the cancer classification for toluene was updated to I, "inadequate information to assess carcinogenic potential," in accordance with EPA's current, 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 1 mg/L to the potential MCLG of 0.06 mg/L.

6.1.35 1,2,4-Trichlorobenzene (CAS# 120-82-1 | DTXSID0021965)

6.1.35.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,2,4-trichlorobenzene on July 17, 1992, establishing both an MCLG and an MCL of 0.07 mg/L{U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.01 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992l, 6574233}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.35.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity for 1,2,4-trichlorobenzene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-105.

Table 6-105. Assessments Identified for 1,2,4-Trichlorobenzene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1992l, 6574233}[d]	0.01	NOAEL	Robinson et al. (1981, 1992847)	–	–	D[e]
EPA OW Health Advisory {U.S. EPA, 1989g, 10532749}	0.00131[f]	NOAEL	Watanabe et al. (1978, 10519464)	–	–	D[e]
WHO GDWQ {WHO, 2004k, 10509449}	0.0077[g]	NOAEL	Côté et al. (1988, 1409067)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
CalEPA PHG {CalEPA, 1999e, 10489836}	NA[h]	NOAEL	Robinson et al. (1981, 1992847)	0.0036	Moore (1994a, 6372408)	–
EPA ORD PPRTV {U.S. EPA, 2009b, 10255709}	Refer to IRIS[i]	–	–	**0.029**	**Moore (1994a, 6372408)**	**L[j]**
ATSDR Toxicological Profile {ATSDR, 2014a, 10254237}	0.1	$BMDL_{10[HED]}$	Moore (1994b, 5926695)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{10[HED]}$ = human equivalent benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Carcinogenicity assessment last revised 1989; oral RfD last revised 1992.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] This oral reference value is based on a 3-month inhalation administration study.

[g] This TDI is for total trichlorobenzenes which consists of three isomers (1,2,3-trichlorobenzene, 1,2,4-trichlorobenzene, and 1,3,5-trichlorobenzene).

[h] CalEPA used a total UF of 10,000 for 1,2,4-trichlorobenzene. A reference value could not be derived since EPA applies a maximum UF of 3,000.

[i] This health assessment defers to the EPA IRIS Chemical Assessment Summary for 1,2,4-trichlorobenzene {U.S. EPA, 1992l, 6574233}.

[j] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2009 EPA ORD PPRTV for 1,2,4-trichlorobenzene {U.S. EPA, 2009b, 10255709} (bolded in Table 6-105) because this is the most recent EPA health assessment that used the best available and most recent science in its evaluation of cancer risk, derived a cancer slope factor, and reported a cancer classification. Although the 2014 ATSDR Toxicological Profile for 1,2,4-trichlorobenzene {ATSDR, 2014a, 10254237} is more recent, it did not derive an oral cancer slope factor. The 1999 CalEPA PHG for 1,2,4-trichlorobenzene {CalEPA, 1999e, 10489836} derived a cancer slope factor based on the same critical study {Moore, 1994a, 6372408} that served as the basis for the cancer slope factor derived in the 2009 EPA ORD PPRTV for 1,2,4-trichlorobenzene {U.S. EPA, 2009b, 10255709}. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals).

The 2009 EPA ORD PPRTV derived a provisional cancer slope factor of 0.029 $(mg/kg/day)^{-1}$ based on a study by Moore (1994a, 6372408). In this study, B6C3F1 mice (50 mice/sex/treatment) were fed diets containing 0, 150, 700, or 3,200 ppm for 104 weeks. Increased incidence of hepatocellular tumors in both sexes was observed, and this outcome was selected as the critical effect for POD derivation. The $BMDL_{10[HED]}$ of 3.5 mg/kg/day for liver tumors in male mice was used to derive the provisional oral slope factor of 0.029 $(mg/kg/day)^{-1}$ based on 10% cancer risk.

EPA described 1,2,4-trichlorobenzene as "likely to be carcinogenic to humans" {U.S. EPA, 2009b, 10255709}, which corresponds to a cancer classification of L based on the 2005 EPA Guidelines for

Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}; therefore, the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.35.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,2,4-trichlorobenzene was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to March 7, 2022.

From this literature search, 33 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 33 unique studies was categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, was excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 32 of the 33 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-106.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,2,4-trichlorobenzene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-106. Evidence Stream Heat Map Results for 1,2,4-Trichlorobenzene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	3
Environmental Fate	–	26
Human	All	4
	Epidemiologic Quantitative Analyses	0
In Vitro	–	8
No Tag	–	2
Total Unique Studies		**32**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.35.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-107 shows the comparison of the basis for the existing and potential MCLGs for 1,2,4-trichlorobenzene.

Table 6-107. Comparison of the Basis for the Existing and Potential MCLGs for 1,2,4-Trichlorobenzene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992l, 6574233)	–	–	–	D	–	–	–	–	–	–
EPA (1992l, 6574233)	Robinson et al. (1981, 1992847)	Increased adrenal weights and vacuolization of the cortex zona fasciculata	–	–	0.01	20%	General Population	70 kg adult, 2 L/day	0.07	–
Relevant Health Assessment Identified in SYR 4										
EPA (2009b, 10255709)	Moore (1994a, 6372408)	Hepatocellular carcinoma in male mice	0.029	L	–	–	General Population	33.8 mL/kg/day	–	0

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.35.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,2,4-trichlorobenzene was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.01 mg/kg/day {U.S. EPA, 1992l, 6574233}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.07 mg/L and assigned 1,2,4-trichlorobenzene a cancer classification of D, "not classifiable as to human carcinogenicity," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2009 EPA ORD PPRTV {U.S. EPA, 2009b, 10255709} to derive the potential MCLG because it is the most recent EPA health assessment and used the best available and most recent science in its derivation of cancer risk, cancer slope factor, and designation of cancer classification. Based on the analysis and conclusion presented in the 2009 EPA ORD PPRTV health assessment, the cancer classification was updated to L, "likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. As there is insufficient information to determine whether 1,2,4-trichlorobenzene has a threshold below which there are no carcinogenic effects, using the linear default extrapolation approach, EPA set the potential MCLG as zero. For 1,2,4-trichlorobenzene, EPA concluded that the available health effects information and the more recent cancer descriptor of L would support lowering the existing MCLG of 0.07 mg/L to zero.

6.1.36 1,1,1-Trichloroethane (CAS# 71-55-6 | DTXSID0021381)

6.1.36.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,1,1-trichloroethane on July 8, 1987, establishing both an MCLG and an MCL of 0.2 mg/L{U.S. EPA, 1987m, 3809376}. EPA based the MCLG on a reference dose of 0.035 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1987ee, 10509764}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.36.2 Results of the SYR 4 Health Assessment Search

The following table shows final health assessments relevant to chronic toxicity available for 1,1,1-trichloroethane that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-108.

Table 6-108. Assessments Identified for 1,1,1-Trichloroethane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985g, 10509761}	–	–	–	–	–	–
EPA OW Health Advisory {U.S. EPA, 1987ee, 10509764}	0.035[d]	LOAEL	McNutt et al. (1975, 93667)	–	–	D[e]
WHO GDWQ {WHO, 2003h, 10709989}	0.6	NOAEL	NTP (2000, 5469437)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile {ATSDR, 2006c, 196129}	20[f]	$BMDL_{10}$	NTP (2000, 5469437)	–	–	–
CalEPA PHG {CalEPA, 2006c, 10489847}	0.076[g]	NOAEL	Rosengren et al. (1985, 95098)	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2007a, 3004991}	**2**	**$BMDL_{10}$**	**NTP (2000, 5469437)**	**–**	**–**	**I[h]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The LOAEL of 250 ppm from an inhalation study was converted to a total absorbed dose of 35 mg/kg/day for use as the POD. The total absorbed dose of 35 mg/kg/day was calculated as follows: [(LOAEL of 250 ppm) × (ventilation volume of 1 m^3/hour for a 70 kg adult) × (6 hours (as the exposure seemed to be saturable, 6 hours was considered to be equivalent to a 24 hour exposure)) × (0.3, the ratio of the administered dose absorbed)/(70 kg, the assumed body weight of an adult)]. The total absorbed dose was then divided by an uncertainty factor of 1,000 to derive this reference value of 0.035 mg/kg/day.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] Intermediate-duration oral MRL; a chronic oral MRL was not derived because chronic-duration oral animal studies were designed as cancer bioassays and included only limited investigation of noncancer endpoints {Maltoni, 1986a, 10510375; NCI, 1977c, 29406}.

[g] Although an RfD was not explicitly calculated in this health assessment, the oral reference value of 0.076 mg/kg/day can be generated from the POD/UF (76 mg/kg/day/1,000) used to derive the PHG. The NOAEL of 70 ppm from an inhalation study was converted to a total absorbed dose of 76 mg/kg/day for use as the POD assuming a breathing rate of 0.032 m^3/day, a body weight of 0.0448 kg, and absorption rate of 30% {CalEPA, 2006c, 10489847}.

[h] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2007 EPA IRIS Toxicological Review of 1,1,1-Trichloroethane {U.S. EPA, 2007a, 3004991} (bolded in Table 6-108) because this is the most recently published EPA health assessment that derives an oral toxicity value and used the best available science, including implementation of BMD modeling. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the 2007 EPA IRIS Toxicological Review, EPA chose a subchronic 13-week feeding study conducted by NTP (2000, 5469437) as the critical study to derive a POD for the chronic oral RfD. In this study, adult F344/N rats and B6C3F1 mice (10 rats or mice/sex/exposure concentration) were fed diets containing 0 (untreated), 0 (placebo microcapsules), 5,000, 10,000, 20,000, 40,000, or 80,000 ppm of microencapsulated 1,1,1-trichloroethane seven days/week for 13 weeks. Significant decreases in terminal body weights (relative to control) were observed in exposed rats (males only) and mice (both sexes); thus, terminal body weight was chosen as the critical effect. Because the body weight data from female mice exhibited the strongest dose-response relationship, these data were used as the basis for the POD. The chronic oral RfD was derived using BMD modeling to calculate the BMD lower limit on a 10% response ($BMDL_{10}$). EPA determined that the $BMDL_{10}$ for decreased terminal body weight in female mice fed 1,1,1-trichloroethane was 2,155 mg/kg/day. A total UF of 1,000 was applied: 10 for interspecies

variability, 10 for intraspecies variation, 3 for extrapolation from subchronic to chronic exposure, and 3 for database deficiencies. After applying the total UF, the chronic oral RfD was calculated to be 2 mg/kg/day.

EPA concluded that the database for 1,1,1-trichloroethane provides "inadequate information to assess carcinogenic potential" according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, based on inadequate evidence of carcinogenicity in humans and animals {U.S. EPA, 2007a, 3004991}.

6.1.36.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,1,1-trichloroethane was defined as one year prior to December 2015, resulting in a search date range from December 1, 2014 to February 24, 2022.

From this literature search, 175 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Two of these 175 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 173 of the 175 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-109.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,1,1-trichloroethane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-109. Evidence Stream Heat Map Results for 1,1,1-Trichloroethane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	52
Environmental Fate	–	86
Human	All	83
	Epidemiologic Quantitative Analyses	13
In Vitro	–	42
No Tag	–	5
Total Unique Studies		**173**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.36.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-110 shows the comparison of the basis for the existing and potential MCLGs for 1,1,1-trichloroethane.

Table 6-110. Comparison of the Basis for the Existing and Potential MCLGs for 1,1,1-Trichloroethane

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987ee, 10509764)	–	–	–	D	–	–	–	–	–	–
EPA (1987ee, 10509764)	McNutt et al. (1975, 93667)	Liver, nervous system, or circulatory problems	–	–	0.035	20%	General Population	70 kg adult, 2 L/day	0.2	–
Relevant Health Assessment Identified in SYR 4										
EPA (2007b, 3004991)	–	–	–	I	–	–	–	–	–	10
EPA (2007a, 3004991)	NTP (2000, 5469437)	Reduced body weight	–	–	2	20%	General Population	33.8 mL/kg/day	–	–

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.36.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,1,1-trichloroethane was published on July 8, 1987 {U.S. EPA, 1987m, 3809376}. Based on an RfD of 0.035 mg/kg/day {U.S. EPA (1987ee, 10509764}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.2 mg/L and assigned 1,1,1-trichloroethane a cancer classification of D, "not classifiable as to human carcinogenicity" according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Toxicological Review of 1,1,1-Trichloroethane {U.S. EPA, 2007b, 3004991} to derive the potential MCLG because this is the most recently published EPA health assessment that derives an oral toxicity value and uses the best available science, including implementation of BMD modeling. Based on an RfD of 2 mg/kg/day, an adjusted DWI-BW value of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 10 mg/L. Based on the analysis and conclusions presented in the 2007 EPA IRIS Toxicological Review, EPA updated the cancer classification for 1,1,1-trichloroethane to I, "inadequate for an assessment of human carcinogenic potential," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that new health effects information supports raising the current MCLG of 0.2 mg/L to the potential MCLG of 10 mg/L.

6.1.37 Toxaphene (CAS# 8001-35-2 | DTXSID7021368)

6.1.37.1 Basis of the Existing MCLG

EPA published the current NPDWR for toxaphene on January 30, 1991 {U.S. EPA, 1991a, 5499}, establishing an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1985h, 3227641}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.003 mg/L based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.1.37.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for toxaphene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-111.

Table 6-111. Assessments Identified for Toxaphene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985h, 3227641}	–[d]	–	–	1.131	Litton Bionetics, Inc. (1978, 673219)	B2[e]
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	–[d]	–	–	–	–	B2[e]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988f, 3123284}	–[d]	–	–	**1.1**	**Litton Bionetics, Inc. (1978, 673219)**	**B2[e]**
EPA OW Health Advisory {U.S. EPA, 1996b, 10492404}	0.0004	NOAEL	Chu et al. (1988, 66099)	Refer to IRIS	NA	B2[e]
CalEPA PHG {CalEPA, 2003e, 3123101}	0.00035[f]	NOAEL	Chu et al. (1986, 66098)	1.2[g]	Litton Bionetics, Inc. (1978, 673219)	–[h]
ATSDR Toxicological Profile {ATSDR, 2014b, 3106211}	0.002[i]	$BMDL_{1SD}$	Tryphonas et al. (2001, 673221)	–	–	–
EPA ORD PPRTV {U.S. EPA, 2018c, 5373923}	0.00009	$BMDL_{10}$ (HED)[j]	Chu et al. (1988, 66099)	Refer to IRIS	Refer to IRIS	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; $BMDL_{1SD}$ = the 95% lower confidence limit on a benchmark response of 1 standard deviation (SD) from the control mean; $BMDL_{10}$(HED) = the 95% lower confidence limit on a benchmark response of 10% using human equivalent doses.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The 1987 EPA OW Drinking Water Criteria and Health Advisory documents state that there were no acceptable studies in the available literature for derivation of a longer-term HA or lifetime Drinking Water Equivalent Level.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] POD/UF was calculated by EPA based on a POD of 0.35 mg/kg/day (NOAEL from a subchronic study in rats) and a total UF of 1,000 reported in the CalEPA PHG.

[g] This cancer potency value was calculated by the Reproductive and Cancer Hazard Assessment Section of California's Office of Environmental Health Hazard Assessment in 1988 {CalEPA, 1988, 10529400}. The PHG assessment states, "New evidence reported since then does not support a change to the potency estimate generated in the 1988 assessment."

[h] This health assessment does not designate a cancer descriptor for toxaphene, but states that "Under California's Proposition 65, toxaphene is considered a substance known to the State to cause cancer."

[i] This value is the intermediate-duration oral MRL. A chronic-duration oral MRL was not derived for toxaphene because (1) no human studies were located regarding the effects of chronic-duration oral exposure to toxaphene, (2) the LOAEL for immune effects identified from intermediate exposure studies in monkeys was lower than the LOAEL for immune effects from chronic exposure studies in monkeys, and (3) toxaphene doses used in chronic oral toxicity studies in rats and mice were two orders of magnitude higher than doses eliciting immunological effects in monkeys treated for chronic and intermediate exposure durations.

[j] The animal doses from the critical study were converted to human equivalent doses (HEDs) prior to benchmark dose modeling using a dosimetric adjustment factor ($BW_{animal}^{1/4} \div BW_{human}^{1/4}$) and a reference human body weight of 70 kg according to guidance in EPA (2011a, 752972).

The health assessment selected for SYR 4 is the 1988 EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988f, 3123284} (bolded in Table 6-111) because this is an EPA health assessment that used the best available science to derive the most health protective cancer slope factor for toxaphene and designated a cancer classification. Although more recent health assessments based on cancer endpoints were available (i.e., EPA ORD PPRTV (2018c, 5373923), CalEPA PHG (2003e, 3123101), and EPA OW Health Advisory (1996b, 10492404)), they did not introduce new science (e.g., the toxicity value was not based on a newer critical study) and/or they reference an older EPA health assessment. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

As reported in the 1988 EPA IRIS Chemical Assessment Summary, EPA selected an 18-month chronic study in mice {Litton Bionetics, Inc., 1978, 673219} as the critical study for dose-response analysis and linear extrapolation of cancer risk. In this study, B6C3F1 mice (54/sex/group) were exposed to 0, 7, 20, or 50 ppm in the diet for 18 months, followed by a six-month observation period. An increased incidence of hepatocellular carcinomas and adenomas in both sexes was observed, but statistical significance was reached only in the 50 ppm males. Thus, the liver tumor data for male mice was selected as the critical effect used to derive the oral slope factor of 1.1 $(mg/kg/day)^{-1}$ using a linearized multistage modeling procedure with "extra risk."

The 1988 EPA IRIS Assessment concluded that toxaphene is a "probable human carcinogen" {U.S. EPA, 1988f, 3123284} which corresponds to a "B2" classification according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Because toxaphene is classified as a "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.37.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA ORD PPRTV {U.S. EPA, 2018c, 5373923} was used to assign the date limit. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for toxaphene was defined as one year prior to July 2018, resulting a search date range from July 1, 2017 to March 9, 2022. From this literature search, 19 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Following SWIFT-Review, all of the 19 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-112.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for toxaphene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-112. Evidence Stream Heat Map Results for Toxaphene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	11
Environmental Fate	–	9
Human	All	11
	Epidemiologic Quantitative Analyses	2
In Vitro	–	7
No Tag	–	1
Total Unique Studies		**19**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.37.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-113 shows the comparison of the basis for the existing and potential MCLGs for toxaphene.

Table 6-113. Comparison of the Basis for the Existing and Potential MCLGs for Toxaphene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1985h, 3227641)	Litton Bionetics, Inc. (1978, 673219)	Hepatocellular carcinomas, neoplastic nodules in male mice	1.1	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (1988f, 3123284)	Litton Bionetics, Inc. (1978, 673219)	Hepatocellular carcinomas, neoplastic nodules in male mice	1.1	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.1.37.5 SYR 4 Health Effects Conclusion

The existing NPDWR for toxaphene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen," for toxaphene {U.S. EPA, 1985h, 3227641} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG to zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988f, 3123284} because it used the best available science to derive the most health protective cancer slope factor for toxaphene. Based on the analysis and conclusion presented in the 1988 EPA health assessment, the cancer classification was maintained at B2. For toxaphene, more recent information does not support a change to the MCLG.

6.1.38 Vinyl Chloride (CAS# 75-01-4 | DTXSID8021434)

6.1.38.1 Basis of the Existing MCLG

EPA published the current NPDWR for vinyl chloride on July 8, 1987 {U.S. EPA, 1987m, 3809376}, establishing an MCLG of zero based on a cancer classification of A, known "human carcinogen" {U.S. EPA, 1987m, 3809376} following EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.002 mg/L, based on analytical feasibility.

6.1.38.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for vinyl chloride that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-114.

Table 6-114. Assessments Identified for Vinyl Chloride

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985i, 76123}	0.0013	NOAEL	Til et al. (1983, 64341)	2.3	Feron et al. (1981, 66030)	–[d]
EPA OW Health Advisory {U.S. EPA, 1987ff, 10532248}	0.0013	NOAEL	Til et al. (1983, 64341)	2.3[f]	Feron et al. (1981, 66030)	A[g]
EPA IRIS Toxicological Review {U.S. EPA, 2000d, 194536}	0.003	$NOAEL_{HED}$	Til et al. (1983, 64341; 1991, 65744)	0.72[h] 1.4[i]	Feron et al. (1981, 66030)	**A[g]**
CalEPA PHG {CalEPA, 2000a, 10489840}	0.0013[e]	NOAEL	Til et al. (1991, 65744)	–[j]	Drew et al. (1983, 79840)	–[k]
WHO GDWQ {WHO, 2004l, 10509452}	–	–	–	–[l]	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile and Addendum {ATSDR, 2006d, 2991431; 2016, 10489757}	0.003	$NOAEL_{HED}$	Til et al. (1983, 64341; 1991, 65744)	–	–	–
HC GDWQ {HC, 2013a, 10528814}	0.009	$NOAEL_{HED}$	Til et al. (1991, 65744)	**0.24**	**Feron et al. (1981, 66030)**	**–[m]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $NOAEL_{HED}$ = the human equivalent external dose corresponding to the NOAEL.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This health assessment does not designate a cancer descriptor based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} but states that "vinyl chloride is a human carcinogen."

[e] POD/UF was calculated by EPA based on a POD of 0.13 mg/kg/day (NOAEL from a chronic oral study in rats) and a UF of 100 reported in the CalEPA PHG.

[f] The cancer slope factor reported in this health assessment was derived by EPA's Carcinogen Assessment Group and was first reported in the EPA OW Drinking Water Criteria Document {U.S. EPA, 1985i, 76123}.

[g] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[h] Oral slope factor based upon the assumption of continuous lifetime exposure beginning at adulthood.

[i] Oral slope factor based upon the assumption of continuous lifetime exposure from birth.

[j] This health assessment did not derive an oral cancer slope factor.

[k] This health assessment does not designate a cancer descriptor based on EPA guidelines for carcinogen risk assessment but reports that vinyl chloride is carcinogenic in animals when given orally or by inhalation. In addition, vinyl chloride exposure via inhalation has been shown to increase the risk of liver cancer in humans, and there is suggestive evidence for cancer of the brain, lung, and digestive tract in humans {CalEPA, 2000a, 10489840}.

[l] This health assessment relies upon the oral slope factors derived by EPA {U.S. EPA, 2000d, 194536} and states that "there is sufficient evidence of the carcinogenicity of vinyl chloride in humans from industrial exposure to high concentrations of vinyl chloride via the inhalation route" and "animal data show vinyl chloride to be a multisite carcinogen."

[m] This health assessment does not designate a cancer descriptor based on EPA guidelines for carcinogen risk assessment but states that "Health Canada classifies vinyl chloride as a Group 1 carcinogen (carcinogenic to humans)."

The health assessments selected for SYR 4 are the 2013 HC GDWQ {HC, 2013a, 10528814} and the EPA IRIS Toxicological Review {U.S. EPA, 2000d, 194536} (bolded in Table 6-114). The HC GDWQ was selected because it is the most recently published health assessment and used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. EPA selected the 2000 IRIS Toxicological Review because it provides a cancer classification for vinyl chloride, which serves as the basis for the MCLG of zero. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

The HC GDWQ employed the most current PBPK model to estimate human equivalent external doses. The EPA IRIS Toxicological Review {U.S. EPA, 2000d, 194536} used the PBPK model developed by Clewell et al. (1995a, 79841; 1995b, 2324991) for derivation of the RfD, and HC further refined this PBPK model developed by Clewell et al. (2001, 192530; 2004, 56269). The oral human slope factor reported by the HC GDWQ was developed using the multistage cancer model in BMDS {U.S. EPA, 2010l, 201615}.

In the 2013 HC GDWQ, a lifespan rat carcinogenicity study by Feron et al. (1981, 66030) was selected as the critical study. In this study, Wistar rats (60–80/sex/group) were fed vinyl chloride at doses of 0, 1.7, 5.0, or 14.1 mg/kg/day for five days/week for 135 weeks in males and 144 weeks in females. Treatment with vinyl chloride induced angiosarcomas and hepatocellular tumors in both male and female rats. PBPK modeling of the external doses from this study was performed to determine the daily internal doses of vinyl chloride metabolites generated per liter of liver tissue for several of the reported cancer endpoints for both male and female rats. HC selected the combined female liver tumors as the critical effect for estimating cancer risk using multistage cancer BMD modeling of these internal doses. Therefore, this endpoint was chosen to determine the POD for calculation of the oral cancer slope factor. The oral human slope factor was then derived using a human PBPK model and was determined to be 0.24 $(mg/kg/day)^{-1}$ {HC, 2013a, 10528814}.

The HC GDWQ does not assign a cancer descriptor. Therefore, the EPA IRIS Toxicological Review for vinyl chloride {U.S. EPA, 2000d, 194536} was selected for its cancer descriptor for vinyl chloride. EPA concluded that vinyl chloride is carcinogenic by a genotoxic mode of action and determined that vinyl chloride is a known "human carcinogen" (cancer descriptor of A) {U.S. EPA, 1986a, 199530}, based on sufficient evidence in humans and experimental animal studies. Because vinyl chloride is classified as a known "human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.1.38.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the ATSDR Toxicological Profile and Addendum was used to assign the date limit {ATSDR, 2006d, 2991431; ATSDR, 2016, 10489757}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for vinyl chloride was defined as one year prior to January 2016, resulting in a search date range from January 1, 2015 to March 25, 2022. From the literature searches performed, a total of 391 unique studies were identified following review of the literature. Following SWIFT-Review, 379 of the 391 unique studies were tagged to the evidence stream categories shown in Table 6-115.

From this literature search, 391 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twelve of these 391 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 379 of the 391 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-115.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for vinyl chloride and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-115. Evidence Stream Heat Map Results for Vinyl Chloride[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	46
Environmental Fate	–	228
Human	All	157
	Epidemiologic Quantitative Analyses	46
In Vitro	–	88
No Tag	–	26
Total Unique Studies		**379**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.38.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-116 shows the comparison of the basis for the existing and potential MCLGs for vinyl chloride.

Table 6-116. Comparison of the Basis for the Existing and Potential MCLGs for Vinyl Chloride

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987m, 3809376	–	–	–	A[d]	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2000d, 194536)	–	–	–	A[d]	–	–	–	–
HC (2013a, 10528814)	Feron et al. (1981, 66030)	Liver tumors in mice	0.24	–	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] This chemical is classified under Category I according to EPA's Cancer Categories Decision Tree.

6.1.38.5 SYR 4 Health Effects Conclusion

The existing NPDWR for vinyl chloride was published on July 8, 1987 {U.S. EPA, 1987m, 3809376}. Based on a cancer classification of A, known "human carcinogen," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG to zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the HC GDWQ {HC, 2013a, 10528814} to derive the potential MCLG because it is the most recently published health assessment, and it used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for vinyl chloride. Although the HC GDWQ does not assign a cancer descriptor, it indicates that there is "sufficient evidence of the carcinogenicity of vinyl chloride in humans from industrial exposure to high concentrations of vinyl chloride via the inhalation route" and "animal data show vinyl chloride to be a multisite carcinogen." The HC description is consistent with EPA's cancer classification of A reported in the EPA IRIS Toxicological Review {U.S. EPA, 2000d, 194536}. Therefore, EPA has maintained the classification of A. For vinyl chloride, more recent information does not support a change to the MCLG.

6.1.39 Xylenes (total) (CAS# 1330-20-7 | DTXSID2021446)

6.1.39.1 Basis of the Existing MCLG

EPA published the current NPDWR for total xylenes on January 30, 1991, establishing an MCLG and an MCL of 10 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 2 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1987gg, 10509767}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.1.39.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for xylenes that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-117.

Table 6-117. Assessments Identified for Xylenes

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987gg, 10509767}	1.79	$NOAEL_{ADJ}$	NTP (1986a, 2342574)	–	–	D[d]
EPA OW Health Advisory {U.S. EPA, 1993f, 10492402}	1.79	$NOAEL_{ADJ}$	NTP (1986a, 2342574)	–	–	D[d]
CalEPA PHG {CalEPA, 1997d, 10489833}	0.25[e]	LOAEL	Uchida et al. (1993, 68636)	–	–	D[d]
EPA IRIS Toxicological Review {U.S. EPA, 2003h, 93129}	0.2	$NOAEL_{ADJ}$	NTP (1986a, 2342574)	–	–	I[f]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2003l, 10509437}	0.179	$NOAEL_{ADJ}$	NTP (1986a, 2342574)	–	–	–[g]
ATSDR Toxicological Profile {ATSDR, 2007d, 737561}	0.2	$NOAEL_{ADJ}$	NTP (1986a, 2342574)	–	–	–
EPA ORD PPRTV {U.S. EPA, 2009f, 1258194}	Refer to IRIS	Refer to IRIS	Refer to IRIS	–	–	–
HC GDWQ {HC, 2014a, 3049488}	**0.013[h]**	**$NOAEL_{HED}$**	**Korsak et al. (1994, 67962)**	–	–	–[i]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; $NOAEL_{ADJ}$ = the no-observed-adverse-effect level adjusted for exposure 5/7 days per week; dash (–) = not provided; $NOAEL_{HED}$ = the human external dose equivalent to the NOAEL; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] The health assessment reported that the POD/UF was calculated by EPA based on a POD of 7.5 mg/kg/day and a total UF of 30. The POD was based on a LOAEL for self-reported neurological symptoms in an occupational study of health effects after inhalation exposure. The LOAEL of 62 mg/m^3 was converted to 7.5 mg/kg/day using a value of 70 kg for adult body weight, an adjustment for 6/7 days/week of exposure, and a value of 10 m^3/day for the volume of air breathed during a working day.

[f] Based on EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999a, 41631}.

[g] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment, but states that "on the basis of the available evidence, xylenes should not be regarded as initiating carcinogens."

[h] The TDI was derived using an inhalation NOAEL from a 3-month study in rats. Physiologically-based pharmacokinetic (PBPK) modeling was employed to estimate an internal xylene blood concentration following inhalation exposure and a human external dose from drinking water required to result in a similar blood concentration.

[i] This health assessment does not designate a cancer descriptor based on EPA's Guidelines for Carcinogen Risk Assessment, but states that "there is insufficient information from both animal and epidemiological studies to determine whether xylenes are carcinogenic in humans."

The health assessment selected for SYR 4 is the 2014 HC GDWQ {HC, 2014a, 3049488} (bolded in Table 6-117) because it derives an oral toxicity value and uses the best available science in its evaluation of non-cancer risk, and it relies on a more recent critical study than previous health assessments In addition, HC utilized data for chronic neurological effects in humans and used PBPK modeling to estimate a human external dose in drinking water. See Section 4.1.2 for the decision-logic that was applied for all SYR 4 chemicals.

In the 2014 HC GDWQ, a three-month inhalation study was chosen to derive a POD for the chronic oral reference value {Korsak, 1994, 67962}. In this study, 12 male Wistar rats/group were exposed via inhalation to 0, 50, or 100 ppm m-xylene for three months. Twenty-four hours after the last exposure, there was decreased rotarod performance in the 100 ppm group. The NOAEL was identified as 50 ppm based on this effect and was used as the POD. PBPK modeling was then used to estimate rat internal blood concentrations (0.138 mg/L for three-month 50 ppm exposure). This value was entered into the human PBPK model to determine the human external dose that would result in blood concentrations similar to the rat. Assuming a drinking water consumption rate of 1.5 L/day, the resulting human external dose ($NOAEL_{HED}$) was calculated to be 1 mg/kg/day. A total uncertainty factor of 75 was applied: 10 for intraspecies variability, 2.5

for interspecies variability, and 3 for extrapolation from subchronic to chronic data. After applying the total uncertainty factor, the tolerable daily intake (TDI) was calculated to be 0.013 mg/kg/day.

The 2014 HC GDWQ does not assign a cancer descriptor for xylene; however, EPA concluded that the evidence for xylene is "inadequate for an assessment of the carcinogenic potential" {U.S. EPA, 2003h, 93129} according to EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}.

6.1.39.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. For the SYR 4 literature search, the EPA SYR 3 Summary Report was used to assign the date limit {U.S. EPA, 2016c, 6557097}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for xylenes was defined as one year prior to December 2015 resulting in a search date range from December 1, 2014 to February 17, 2022. From this literature search, 1,413 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Ninety-six of these 1,413 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,317 of the 1,413 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-118.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for xylenes and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-118. Evidence Stream Heat Map Results for Xylenes[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	318
Environmental Fate	–	456
Human	All	616
	Epidemiologic Quantitative Analyses	124
In Vitro	–	344
No Tag	–	12
Total Unique Studies		1,317

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.1.39.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-119 shows the comparison of the basis for the existing and potential MCLGs for xylenes.

Table 6-119. Comparison of the Basis for the Existing and Potential MCLGs for Xylenes

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987gg, 10509767)	–	–	–	D	–	–	–	–	–	–
EPA (1987gg, 10509767)	NTP (1986a, 2342574)	Decreased body weight gains	–	–	2	20%	General Population	70 kg adult, 2 L/day	10	–
Relevant Health Assessments Identified in SYR 4										
EPA (2003h, 93129)	–	–	–	I	–	–	–	–	–	–
HC (2014a, 3049488)	Korsak et al. (1994, 67962)	Decrease performance of male rats on the rotarod test (a measure of motor coordination disturbances indicative of adverse neuromuscular effects)	–	–	0.013[d,e]	20%	General Population	33.8 mL/kg/day	–	0.08

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] Derived from a POD using a UF_A applied according to IPCS guidance (2005, 198739) to apportion the UF_A (4) to toxicokinetics and 2.5× to toxicodynamics. EPA's guidance also recognizes that the UF_A can be divided into a toxicokinetic and toxicodynamic portion but apportions 3× to each. The HC GDWQ utilized a PBPK model in deriving the POD. According to both IPCS (2005, 198739) and EPA (bodyweight)$^{3/4}$ allometric scaling guidance {U.S. EPA, 2011a, 752972}, the toxicokinetic portion of the UF_A can be reduced to one, leaving only the toxicodynamic portion. EPA policy would be to apply a 3× UF_A in this circumstance, but HC applies a value of 2.5× according to IPCS guidance (2005, 198739). Given that the HC RfV is a peer-reviewed document citing an accepted risk assessment guidance, EPA has chosen to calculate the potential MCLG based on the HC RfV of 0.013 mg/kg/day (2014a, 3049488) while acknowledging that a decision to revise the existing xylenes MCLG would likely follow EPA's existing guidance.

[e] PBPK modeling was employed to estimate an internal blood concentration following inhalation exposure.

6.1.39.5 SYR 4 Health Effects Conclusion

The existing NPDWR for total xylenes was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 2 mg/kg/day {U.S. EPA, 1987gg, 10509767}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 10 mg/L and assigned xylenes a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1987gg, 10509767}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the HC GDWQ {HC, 2014a, 3049488} to derive the potential MCLG because it derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk, as it relies on a more recent critical study than the previous health assessments. Based on an RfD of 0.013 mg/kg/day{HC, 2014a, 3049488}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.08 mg/L. Based on the analysis and conclusion presented in the EPA IRIS Toxicological Review {U.S. EPA, 2003h, 93129}, the cancer classification for total xylenes was updated to I, "inadequate information to assess carcinogenic potential," in accordance with EPA's 1999 Draft Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 10 mg/L to the potential MCLG of 0.08 mg/L.

6.2 TSCA Chemicals

6.2.1 Asbestos (fiber > 10 micrometers) (CAS# 1332-21-4 | DTXSID4023888)

6.2.1.1 Basis of the Existing MCLG

EPA published the current NPDWR for asbestos on January 30, 1991, establishing both an MCLG and an MCL of 7 million fibers/L (MFL) for fibers exceeding 10 micrometers in length {U.S. EPA, 1991a, 5499; U.S. EPA, 1988a, 10714957}. Due to limited available evidence for carcinogenicity after oral exposure to asbestos, EPA considered asbestos as a Category II contaminant for the oral exposure route {U.S. EPA, 1991a, 5499} (see Table 3-1 for more information on cancer classification). For the NPDWR, EPA used an excess cancer risk approach to derive the MCLG for several reasons including the availability of dose response data for benign polyps that could be used to derive a CSF, limited noncancer data after oral exposure, and the assumption that asbestos could cause cancer after oral exposure based on its designation as a Group A human carcinogen through inhalation exposure {U.S. EPA, 1991a, 5499}. The MCLG for asbestos was based on evidence of benign polyps occurring in male rats following oral administration to intermediate size (e.g., greater than 10 micrometers) chrysotile fibers in an oral study by NTP {NTP, 1985c, 758884}. Based on a CSF of 1.4×10^{-13} $(\text{fibers/L})^{-1}$ derived from the NTP (1985c, 758884) ingestion study of chrysotile fibers, DWI and BW values for the general population (i.e., 2 L/day and 70 kg, respectively), and a 10^{-6} excess cancer risk, EPA set the MCLG at 7 million fibers/L (MFL) {U.S. EPA, 1988a, 10714957}.

6.2.1.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for asbestos that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-120.

Table 6-120. Assessments Identified for Asbestos

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988a, 10714957}	–	–	–	**1.4×10^{-13}[d]**	**NTP (1985c, 758884)**	**A[e]**
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1988j, 783514}	–[f]	–	–	–	–	A[e]
HC GDWQ {HC, 1989, 10606117}[g]	–	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2001b, 786664}	–[h]	–	–	–	–	–
CalEPA PHG {CalEPA, 2003f, 3982252}	3.35×10^{8}[i]	LOAEL	Cemerikic (1977, 3649921)	1.4×10^{-13}[d,j]	NTP (1985c, 758884)	–
WHO GDWQ {WHO, 2003m, 10605374}	–	–	–	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2014, 9109843}[k]	–	–	–	–	–	H[l]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in fibers/kg/day unless otherwise specified; "oral reference value" refers to the point of departure/uncertainty factor (POD/UF).

[c] Cancer slope factors expressed in $(\text{fibers/L})^{-1}$ unless otherwise specified.

[d] This health assessment derived a cancer potency value as a drinking water concentration of 1.4×10^{-13} $(\text{fibers/L})^{-1}$ based on a 70-kg adult consuming 2 L of drinking water per day.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The reference dose for oral exposure for asbestos was not assessed under the IRIS program {U.S. EPA, 1988j, 783514}.

[g] This HC GDWQ document for asbestos was drafted in February 1986, edited in March 1989, and "reaffirmed" in 2005 according to a summary table in Guidelines for Canadian Drinking Water Quality available at https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html.

[h] An oral cancer slope factor was not determined. No minimal risk levels (MRLs) were derived for oral asbestos exposure. There were no available studies on noncancer health effects in humans orally exposed to asbestos fibers, and the ATSDR Toxicological Profile for asbestos states that the weight of evidence for chronic oral animal studies indicates that oral exposure to asbestos does not cause any significant noncarcinogenic effects.

[i] RfV calculated based on a POD of 107 mg/kg/day, CalEPA's conversion rate of 9.4×10^{9} fibers/mg, and CalEPA's UF of 3,000.

[j] The analysis in the CalEPA PHG was reproduced from EPA (1985j, 759183).

[k] This health assessment is specific to Libby Amphibole asbestos. The term "Libby Amphibole asbestos" references the mixture of amphibole mineral fibers of varying elemental composition (e.g., winchite, richterite, tremolite) that have been identified in the Rainy Creek complex near Libby, MT. An oral RfD or CSF was not derived because "inhalation is the primary route of concern and oral information for Libby Amphibole asbestos is lacking." The cancer descriptor is based on the weight of evidence for inhalation exposures {U.S. EPA, 2014, 9109843}.
[l] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as asbestos. However, the OPPT Risk Evaluation for Asbestos: Chrysotile Asbestos (Part 1) was finalized in December 2020 {U.S. EPA, 2020c, 7697235} which is after the SYR 4 cut-off date of November 2020 that was used for the health assessment identification process. The Risk Evaluation of Asbestos, Part 2: Supplemental Evaluation including Legacy Uses and Associated Disposals of Asbestos is ongoing and is expected to be finalized by December 2024. Therefore, Parts 1 and 2 (if available) of the OPPT Risk Evaluation for Asbestos will be considered in the next SYR cycle (SYR 5).

Since the OPPT risk evaluation was not finalized by the SYR 4 cut-off date, the most recent health assessments from other sources were considered. Among the health assessments identified, the OW Drinking Water Criteria Document is the only final health assessment that derived an oral CSF for asbestos {U.S. EPA, 1988a, 10714957}. The other available health assessments either did not report an oral toxicity value (IRIS Chemical Assessment Summary {U.S. EPA, 1988j, 783514}; IRIS Toxicological Review {U.S. EPA, 2014, 9109843}), reported no value (HC Drinking Water Guideline {HC, 1989, 10606117}, ATSDR Toxicological Profile {ATSDR, 2001b, 786664}; WHO GDWQ {WHO, 2003l, 10509437}), or relied on the oral CSF derived by EPA {CalEPA, 2003, 3982252}. The California EPA PHG {CalEPA, 2003f, 3982252} also derives a noncancer oral reference value for asbestos; however, the critical study used to derive the reference value predates the available EPA health assessments and, thus, does not introduce new science. Therefore, the health assessment selected for SYR 4 is the 1988 OW Drinking Water Criteria Document {U.S. EPA, 1988a, 10714957}.

The 1988 OW Drinking Water Criteria Document derived a human CSF for asbestos of 1.4×10^{-13} $(\text{fibers/L})^{-1}$ {U.S. EPA, 1988a, 10714957} based on findings from the 1985 draft NTP report on chrysotile fibers {NTP, 1988, 3613439}. The health assessment bases the CSF and 10^{-6} cancer risk on a critical study with oral exposure to chrysotile asbestos (CASRN 12001-29-5) {NTP, 1988, 3613439}. In the NTP dietary feeding study, no evidence of carcinogenicity was observed in rats after exposure to the short-range fibers. However, exposure of rats at 1% in the diet (10,000 mg/kg) to intermediate-range fibers resulted in benign epithelial neoplasms in the large intestine of male rats. The NTP 1985 study describes these benign epithelial neoplasms as adenomatous polyps which NTP considered to provide some evidence of carcinogenicity in male rats exposed to chrysotile asbestos {NTP, 1988, 3613439}. In the selected health assessment, the dietary dose of asbestos was extrapolated to a drinking water dose of 500 mg/kg/day. The drinking water dose was converted to the number of asbestos fibers/body weight/day, yielding 6.45×10^{10} fibers/kg/day. Extrapolating this to a human equivalent dose, assuming an adult body weight of 70 kg, resulted in 1.13×10^{10} fibers/kg/day {U.S. EPA, 1988a, 10714957}. The cancer potency estimate was then calculated, assuming a body weight of 70 kg and a daily water intake of 2 liters, and the estimation resulted in a 95% upper-limit potency of 1.4×10^{-13} $(\text{fibers/L})^{-1}$ for asbestos.

In the health assessment, EPA describes asbestos as a Group A human carcinogen, "carcinogenic to humans" {U.S. EPA, 1988a, 10714957}, via all routes of exposure under EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. This is based on findings of lung cancer and mesothelioma after exposure to all major types of asbestos. The human evidence of gastrointestinal carcinogenicity, based on inhalation epidemiology studies, is moderate and is consistent with some evidence of stomach and pancreas cancer from ingestion epidemiology studies. Animal studies with exposure via either the inhalation or oral routes support the human evidence for asbestos carcinogenicity

{U.S. EPA, 1985j, 759183}. It is important to note that while the available health assessments categorize asbestos as a Group A human carcinogen, "carcinogenic to humans," EPA treated asbestos as a Category II, or Group C, contaminant for the oral exposure route in the NPDWR for asbestos due to limited available evidence for carcinogenicity after oral exposure {U.S. EPA, 1991a, 5499}. Because asbestos is classified as "carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.1.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search conducted for the OPPT Draft Scope of the Risk Evaluation for Asbestos, which had a cut-off date of April 2021. The Final Scope of the Risk Evaluation for Asbestos Part 2 literature search was conducted in September 2021 {U.S. EPA, 2022d, 10661454}; however, this was not available at the time of the SYR 4 literature search and is therefore not included here. The start date of the SYR 4 literature search update conducted in PubMed and Web of Science for asbestos was defined as one year prior to April 2021, the cut-off date for the OPPT risk evaluation, resulting in a literature search date range of April 1, 2020 to September 9, 2022.

From this literature search, 622 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Ten of these 622 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 612 of the 622 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-121.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for asbestos and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-121. Evidence Stream Heat Map Results for Asbestos[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	91
Environmental Fate	–	48
Human	All	543
	Epidemiologic Quantitative Analyses	168
In Vitro	–	179
No Tag	–	26
Total Unique Studies		**612**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.1.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-122 shows the comparison of the basis for the existing and potential MCLGs for asbestos.

Table 6-122. Comparison of the Basis for the Existing and Potential MCLGs for Asbestos

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[a]	Potential MCLG[a,b]
Basis of Regulation									
EPA (1988a 10714957)	NTP (1985c, 758884)	Increased risk of developing benign intestinal polyps in rats	1.4×10^{-13} $(\text{fibers/L})^{-1}$	A	–	General Population	70 kg adult, 2 L/day	7 MFL[c]	–
Relevant Health Assessment Identified in SYR 4									
EPA (1988a, 10714957)	NTP (1985c, 758884)	Increased risk of developing benign intestinal polyps in rats	1.4×10^{-13} $(\text{fibers/L})^{-1}$	A	–	General Population	70 kg adult, 2 L/day[d]	–	7 MFL[c]

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Values expressed in mg/L unless otherwise specified.
[b] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[c] For asbestos, EPA has set the MCLG based upon a theoretical lifetime excess cancer risk of 10^{-6} using the CSF derived from NTP (1985, 758884).
[d] Calculation of CSF relies on 2/3 body weight scaling of the dose from animal to humans. In this instance, the exposure factors cannot be updated to L/kg/day; therefore, the original exposure factors were applied.

6.2.1.5 SYR 4 Health Effects Conclusion

The existing NPDWR for asbestos was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an excess cancer risk of 10^{-6}, a CSF of 1.4×10^{-13} (fibers/L)$^{-1}$ and DWI and BW values for the general population (i.e., 2 L/day and 70 kg), EPA set the MCLG at 7 million fibers/L (MFL). Due to limited available evidence for carcinogenicity after oral exposure to asbestos, EPA regulated asbestos as a Category II contaminant, equivalent to a possible human carcinogen by the oral route of exposure {U.S. EPA, 1991a, 5499}. For the NPDWR, EPA used an excess cancer risk approach to derive the MCLG because there were quantitative data to derive a CSF based on benign polyps, there were limited noncancer data for asbestos after exposure via the oral route, and it was assumed that asbestos could cause cancer through oral exposure based on its designation as a Group A human carcinogen through inhalation exposure {U.S. EPA, 1991a, 5499}. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the same health assessment on which the MCLG in the NPDWR was based, the EPA OW Drinking Water Criteria Document {U.S. EPA, 1985j, 759183; U.S. EPA, 1988a, 10714957}, to derive the potential MCLG. Based on a 10^{-6} excess cancer risk, a CSF of 1.4×10^{-13} (fibers/L)$^{-1}$, and DWI and BW values for the general population (i.e., 2 L/day and 70 kg, respectively {U.S.EPA, 2000, 19428}), EPA calculated a potential MCLG of 7 million fibers/L (MFL). EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 7 million fibers/L (MFL) based on human health effects.

6.2.2 Carbon tetrachloride (CAS# 56-23-5 | DTXSID8020250)

6.2.2.1 Basis of the Existing MCLG

EPA published the current NPDWR for carbon tetrachloride on July 8, 1987 {U.S. EPA 1985m, 3809376}. The NPDWR established an MCLG of zero based on evidence of carcinogenicity {U.S. EPA 1985d, 3809374}. Carbon tetrachloride is classified as a Group B2 carcinogen due to sufficient evidence of carcinogenicity in animals and inadequate evidence in humans {U.S. EPA 1985d, 3809374, according to EPA's 1986 Proposed Guidelines for Carcinogen Risk Assessment, {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L, based on analytical feasibility {U.S. EPA 1987m, 3809376}.

6.2.2.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for carbon tetrachloride that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-123.

Table 6-123. Assessments Identified for Carbon Tetrachloride

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987hh, 10605330}	0.0007[d]	NOAEL	Bruckner et al. (1986, 62379)	–	–	B2[e]
CalEPA PHG {CalEPA, 2000b, 10489863}	0.0007[f]	NOAEL	Bruckner et al. (1986, 62379)	–[g]	–	–
WHO GDWQ {WHO, 2004m, 3838547}	0.0014[h]	NOAEL	Bruckner et al. (1986, 62379)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile {ATSDR, 2005b, 195104}	0.007[i]	NOAEL	Bruckner et al. (1986, 62379)	–[j]	–	–
HC GDWQ {HC, 2010b, 3827285}	0.00071	NOAEL	Bruckner et al. (1986, 62379)	–	–	–
EPA IRIS Chemical Assessment Summary {U.S. EPA, 2010f, 3490869}	0.004	$BMDL_{2\times\text{-ADJ}}$	Bruckner et al. (1986, 62379)	**0.07[k]**	**Nagano et al. (2007, 194127); JBRC (1998, 194128)**	**L[l]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{2\times\text{-ADJ}}$ = benchmark dose, 95% lower bound (corresponding to an increase in sorbitol dehydrogenase activity 2 times the control mean, adjusted by a factor of 5/7).

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The RfD was calculated by EPA as 0.050 mg/day assuming an adult body weight of 70 kg. The oral toxicity value reported here is calculated from the POD (NOAEL, 1 mg/kg/day), the uncertainty factors (total UF: 1,000), and an adjustment of 5/7 to account for the weekly oral gavage regimen.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] This value is the POD/UF. The POD is the adjusted NOAEL (1 mg/kg/day), which was modified by a factor of 5/7 to account for a dosing regimen of 5 days/week used in the critical study. An uncertainty factor of 1,000 was used.

[g] This assessment did not derive its own CSF but relied on a cancer potency value of 0.18 $(mg/kg/day)^{-1}$ (developed by the California Public Health Foundation {Reed et al., 1988, 10534157} and based on analysis of data from Edwards et al. (1942, 6090)) to develop a health-protective concentration for carcinogenic effects.

[h] This assessment cites International Programme on Chemical Safety {IPCS, 1999, 3001090} as the basis for the TDI calculation.

[i] Intermediate-duration oral MRL; a chronic oral MRL was not derived because serious effects were observed at the lowest doses tested in chronic oral bioassays in rats and mice. A no-observed-effect level was not identified in the available chronic oral studies, and ATSDR does not base MRLs on doses at which serious effects occur.

[j] This assessment did not derive its own CSF but reports an oral slope factor of 0.13 $(mg/kg/day)^{-1}$ derived by EPA (no citation provided).

[k] Physiologically based pharmacokinetic modeling was applied to extrapolate inhalation tumor data to the oral route.

[l] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as carbon tetrachloride. The OPPT risk evaluation for carbon tetrachloride was considered during SYR 4 because it was finalized by the SYR 4 cut-off date, in November 2020 {U.S. EPA, 2020d, 7697236}. However, the health assessment selected for SYR 4 is the IRIS Chemical Assessment Summary for Carbon Tetrachloride {U.S. EPA, 2010f, 3490869} because it is the only available assessment that derives a cancer slope factor for carbon tetrachloride for the oral route of exposure. The IRIS EPA health assessment derived an oral CSF from the inhalation data using a PBPK model {U.S. EPA, 2010f, 3490869}. Although the OPPT Risk Evaluation is a more recent assessment for carbon tetrachloride and derived an inhalation risk unit based on the same critical study as the IRIS Chemical Assessment Summary, it did not derive an oral CSF for these data {U.S. EPA, 2020d, 7697236}.

In the IRIS Chemical Assessment Summary, a two-year chronic study in male and female F344 rats and BDF1 mice {Nagano, 2007, 194127; JBRC, 1998, 194128} was selected as the critical study for linear extrapolation of cancer risk. Because studies on carcinogenicity by the oral route were not adequate for dose-response analysis, inhalation data were used to determine the oral slope factor for carbon tetrachloride. In the chronic study, rats and mice (50/sex/dose) were exposed to 0, 5, 25, or 125 ppm (32, 160, or 801 mg/m^3) carbon tetrachloride for 6 hours/day, 5 days/week, for 2 years via inhalation {Nagano, 2007, 194127; JBRC, 1998, 194128}. Incidences of hepatocellular adenomas and carcinomas were increased in rats and mice of both sexes, and incidences of adrenal pheochromocytomas were increased in mice of both sexes. The IRIS Chemical Assessment Summary estimated the oral cancer slope factor using the tumor data from this inhalation study and PBPK modeling to extrapolate from the inhalation to oral route and between species {U.S. EPA, 2010f, 3490869}.

The highest oral cancer slope factor determined was for hepatocellular adenomas or carcinomas in female mice ($0.07\ (mg/kg/day)^{-1}$) and was selected by EPA as the most scientifically defensible. In brief, inhalation exposure concentrations were converted to estimated internal doses by applying a mouse PBPK model followed by multistage BMD modeling to derive the $BMDL_{10}$ for liver tumor data in female mice. This $BMDL_{10}$ was then extrapolated from mice to humans, again using PBPK modeling, to derive HEDs. The average of these HED values, 1.54 mg/kg/day, was used as the POD to derive the oral cancer slope factor of $0.07\ (mg/kg/day)^{-1}$ based on 10% cancer risk {U.S. EPA, 2010f, 3490869}.

In the IRIS Chemical Assessment Summary, EPA followed the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976} to determine that carbon tetrachloride is "likely to be carcinogenic in humans" based on inadequate evidence of carcinogenicity in humans and sufficient evidence in animals by oral and inhalation exposure {U.S. EPA, 2010f, 3490869}. Because of this classification, the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.2.3 SYR 4 Literature Search Results.

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Risk Evaluation for Carbon Tetrachloride which was March 2017 {U.S. EPA, 2020d, 7697236}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for carbon tetrachloride was defined as one year prior to March 2017, resulting in a search date range from March 1, 2016 to September 28, 2022.

From this literature search, 2,195 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Fourteen of these 2,195 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 2,181 of the 2,195 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-124.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for carbon tetrachloride and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-124. Evidence Stream Heat Map Results for Carbon Tetrachloride[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1,956
Environmental Fate	–	202
Human	All	954
	Epidemiologic Quantitative Analyses	23
In Vitro	–	1,569
No Tag	–	22
Total Unique Studies		**2,181**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.2.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-125 shows the comparison of the basis for the existing and potential MCLGs for carbon tetrachloride.

Table 6-125. Comparison of Existing and Potential MCLGs for Carbon Tetrachloride

Reference	Critical Study	Critical Effect	Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1985d, 3809374)	–	–	–	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2010f, 3490869)	Nagano et al. (2007, 194127); JBRC (1998, 194128)	Liver tumors and pheochromocytomas	0.07	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.2.5 SYR 4 Health Effects Conclusion

The existing NPDWR for carbon tetrachloride was published on November 13, 1985 {U.S. EPA, 1985d, 3809374}. Based on a cancer classification of B2, "probable human carcinogen," EPA set the MCLG at zero {U.S. EPA, 1985d, 3809374}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the IRIS Chemical Assessment Summary {U.S. EPA, 2010f, 3490869} because it is the only available assessment that derives a cancer slope factor for carbon tetrachloride for the oral route of exposure. Based on the analysis and conclusion presented in this health assessment, the CSF was set at 0.07 $(mg/kg/day)^{-1}$ and the cancer classification for carbon tetrachloride was updated to L, "likely to be carcinogenic to humans" {U.S. EPA, 2010f, 3490869}, according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For carbon tetrachloride, more recent information does not support a change to the MCLG.

6.2.3 1,2-Dichlorobenzene (o-Dichlorobenzene) (CAS# 95-50-1 | DTXSID6020430)

6.2.3.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,2-dichlorobenzene on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established both an MCLG and an MCL of 0.6 mg/L{U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.09 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1988d, 10520442}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.2.3.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for 1,2-dichlorobenzene (also called o-dichlorobenzene) that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-126.

Table 6-126. Assessments Identified for 1,2-Dichlorobenzene (o-Dichlorobenzene)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987ii, 5020212}	0.089[d]	NOAEL	NTP (1985a, 10489888)	–	–	D[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1988d, 10520442}	0.09[f]	NOAEL	NTP (1985a, 10489888)	–	–	–
HC GDWQ {HC, 1988, 5099080}	0.021[g]	LOAEL	NTP (1985a, 10489888)[h]	–	–	–[i]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1989h, 5099072}[j]	0.09[k]	NOAEL	NTP (1985a, 10489888)	–	–	D[e]
WHO GDWQ {WHO, 2003n, 10509428}	0.429[l]	NOAEL	NTP (1985a, 10489888)[m]	–	–	–
ATSDR Toxicological Profile {ATSDR, 2006a, 5160103}	**0.3[n]**	**$BMDL_{10\ ADJ}$**	**NTP (1985a, 10489888)**	–	–	–
CalEPA PHG {CalEPA, 2009b, 10489850}[o]	0.089[p]	NOAEL	NTP (1985a, 10489888)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{10\ ADJ}$ = benchmark dose at the 95% lower confidence limit on a 10% response adjusted for intermittent exposure (5 days/7 days).

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This RfD was derived using a NOAEL of 125 mg/kg/day from subchronic studies in rats and mice.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] This RfD was derived using a NOAEL of 120 mg/kg/day from chronic studies in rats and mice. This assessment reports the RfD as 6 mg/day, which is converted to 0.086 mg/kg/day using the default body weight of 70 kg.

[g] This ADI was derived using a LOAEL of 30 mg/kg/day and a conversion of 5 days per week of dosing to 7 days per week from a subchronic study in rats.

[h] This health assessment cites the draft version of the NTP report {NTP, 1982b, 10489886}, but it is cited here as the final document {NTP, 1985a, 10489888}.

[i] This health assessment does not provide a cancer descriptor based on EPA's cancer guidelines, but states that 1,2-dichlorobenzene is included in Group VA (inadequate data for evaluation).

[j] RfD assessment last revised 1989 {U.S. EPA, 1989h, 5099072}; carcinogenicity assessment last revised 1990.

[k] This RfD was derived using a NOAEL of 120 mg/kg/day (adjusted to 85.7 mg/kg/day) from a chronic study in rats.

[l] This TDI was derived using a NOAEL of 60 mg/kg/day from a chronic study in mice.

[m] This health assessment cites WHO {1991, 81628}, which cites the NTP (1985a, 10489888) report as the source of the data.

[n] This chronic oral MRL was derived using BMD analysis conducted on data from a chronic study in mice.

[o] The CalEPA PHG was published in 1997 {CalEPA, 1997e, 10489795} with a memorandum update in 2009. In the 2009 memorandum update, CalEPA re-evaluated the available data, including the BMD analysis done by ATSDR (2006a, 5160103) and several new studies, and determined that a complete update and revision of the PHG document was unnecessary.

[p] POD/UF was calculated by EPA based on a POD of 125 mg/kg/day (NOAEL from a subchronic study in rats), adjusting for discontinuous exposure (5 days/7 days), and using a UF of 1,000.

Following the decision-logic provided in the assessment selection criteria (see Section 4.1.2), final OPPT risk evaluations are preferred for regulated industrial chemicals such as 1,2-dichlorobenzene/o-dichlorobenzene. However, the OPPT risk evaluation for o-dichlorobenzene is ongoing (the Final Scope of the Risk Evaluation for o-Dichlorobenzene was finalized in August of 2020). Since the OPPT risk evaluation was not finalized by the SYR 4 cut-off date of November 2020, it was not selected. If finalized by the SYR 5 cut-off date for identifying assessments, then it will be considered in the next SYR cycle (SYR 5).

The health assessment selected for SYR 4 is the ATSDR Toxicological Profile (2006a, 5160103) for 1,2-dichlorobenzene (1,2-DCB) (bolded in Table 6-126) because it derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk, including application of an updated modeling approach to derive a RfD. Although a more recent health assessment was available (CalEPA's PHG {CalEPA, 2009b, 10489850}), it was based on the same critical study as the selected ATSDR Toxicological Profile (2006a, 5160103) and used a NOAEL instead of a BMD modeling approach.

In the ATSDR Toxicological Profile, a chronic oral toxicity study conducted by NTP (1985a, 10489888) was selected to derive a POD for the chronic oral RfD. In this study, groups of F344/N rats and B6C3F1 mice (50/sex/dose/species) were administered 1,2-DCB in corn oil by gavage in doses of 0, 60, or 120 mg/kg/day for 5 days/week for 103 weeks. An exposure-related increase in the incidence of renal tubular regeneration in male mice was observed in the high dose group. To derive an MRL, BMD analysis was conducted using the kidney lesion incidence data, resulting in a benchmark dose lower limit ($BMDL_{10}$) of 43.04 mg/kg/day. This $BMDL_{10}$ of 43.04 mg/kg/day was then adjusted for intermittent experimental exposure (5 days/7 days) to give a duration-adjusted $BMDL_{10}$ of 30.74 mg/kg/day. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF to the duration adjusted POD, the chronic oral MRL was calculated to be 0.3 mg/kg/day.

The ATSDR Toxicological Profile does not assign a cancer descriptor for 1,2-DCB; however, EPA categorized 1,2-DCB as Group D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1989h, 5099072}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on the available animal data and lack of data on possible carcinogenic effects in humans.

6.2.3.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for 1,2-dichlorobenzene which was May 2019 {U.S. EPA, 2020e, 10617338}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,2-dichlorobenzene was defined as one year prior to May 2019 resulting in a search date range from May 1, 2018 to September 23, 2022.

From this literature search, 240 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Nine of these 240 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 231 of the 240 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-127.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,2-dichlorobenzene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-127. Evidence Stream Heat Map Results for 1,2-Dichlorobenzene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	25
Environmental Fate	–	62
Human	All	155
	Epidemiologic Quantitative Analyses	4
In Vitro	–	53
No Tag	–	8
Total Unique Studies		**231**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.3.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-128 shows the comparison of the basis for the existing and potential MCLGs for 1,2-dichlorobenzene (o-dichlorobenzene).

Table 6-128. Comparison of the Basis for the Existing and Potential MCLGs for 1,2-Dichlorobenzene (o-Dichlorobenzene)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1988d, 10520442)	–	–	–	D	–	–	–	–	–	–
EPA (1988d, 10520442)	NTP (1985a, 10489888)[d]	Renal and hepatic lesions, lower BW, increased uroporphyrin and coproporphyrin levels in rats and mice	–	–	0.09	20%	General Population	70 kg adult, 2 L/day	0.6	–
Relevant Health Assessments Identified in SYR 4										
EPA (1989h, 5099072)	–	–	–	D	–	–	–	–	–	–
ATSDR (2006a, 5160103)	NTP (1985a, 10489888)[e]	Incidence of renal tubular regeneration in male mice	–	–	0.3	20%	General Population	33.8 mL/kg/day	–	2

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable; BW = birth weight.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] The RfV was calculated based on a subchronic study in rats and mice.
[e] The RfV was calculated based on a chronic study in mice.

6.2.3.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,2-dichlorobenzene (o-dichlorobenzene) was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.09 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.6 mg/L and assigned 1,2-dichlorobenzene a cancer descriptor of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1988d, 10520442}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2006 ATSDR Toxicological Profile {ATSDR, 2006a, 5160103} to derive the potential MCLG because it derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk, including application of an updated modeling approach to derive an RfD. Based on an RfD of 0.3 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 2 mg/L. Although the ATSDR Toxicological Profile did not provide a cancer descriptor, based on the analysis and conclusion presented in this and earlier health assessments, EPA maintained the cancer classification for 1,2-dichlorobenzene at D, "not classifiable as to human carcinogenicity," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA concluded that new health effects information supports raising the current MCLG of 0.6 mg/L to the potential MCLG of 2 mg/L.

6.2.4 1,4-Dichlorobenzene (p-Dichlorobenzene) (CAS# 106-46-7 | DTXSID1020431)

6.2.4.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,4-dichlorobenzene on July 8, 1987 {U.S. EPA, 1987m, 3809376}. The NPDWR established both an MCLG and an MCL of 0.075 mg/L. EPA based the MCLG on a reference dose of 0.1 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1987ii, 5020212}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. A risk management safety factor of 10 was applied in the calculation of the MCLG to account for possible carcinogenicity {U.S. EPA, 1987m, 3809376} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.2.4.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for 1,4-dichlorobenzene (p-dichlorobenzene) that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-129**.**

Table 6-129. Assessments Identified for 1,4-Dichlorobenzene (p-Dichlorobenzene)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987ii, 5020212}	0.1	NOAEL[d]	NTP (1987, 2961751)[e]	–[f]	–	C[g]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1984c, 10532592}	0.107[h]	NOAEL	Battelle (1980, 4929933); NTP (1987, 2961751)	–[i]	–	C[g]
HC GDWQ {Health Canda, 1988, 5099080}	–	–	–	–	–	–[j]
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1994b, 5160168}	–	–	–	–	–	–
CalEPA PHG {CalEPA, 1997f, 5155646}	0.0188	NOAEL	Hollingsworth et al. (1956, 3647)	0.0054	NTP (1987, 2961751)	–
WHO GDWQ {WHO, 2003n, 10509428}	0.107	LOAEL	NTP (1987, 2961751)[k]	–	–	–
ATSDR Toxicological Profile {ATSDR, 2006a, 5160103}	**0.07**	**$BMDL_{1SD}$**	**Naylor and Stout (1996, 5017705)**	–	–	–
EPA OPP RED {U.S. EPA, 2008e, 10509481}	–	–	–	–	–	L/N[l]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; OW = Office of Water; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level; $BMDL_{1SD}$ = lower 95% confidence limit on the benchmark response of 1 standard deviation change in the control mean.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The EPA OW Health Advisory notes that a subchronic NOAEL from a study in rats was identified as the POD because it was higher than the NOAEL in the available chronic rodent study by Hollingsworth et al. (1956, 3647).

[e] The EPA OW Health Advisory cites a "galley draft" 1986 version of the NTP (1987, 2961751) study.

[f] The EPA OW Health Advisory does not calculate a CSF but reports a CSF of 0.02 $(mg/kg/day)^{-1}$ and cites EPA (1986e, 10509763) as the source.

[g] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[h] This health assessment reports an RfD of 7.5 mg/day (derived using a NOAEL of 150 mg/kg/day from a subchronic study in rats), which is converted to 0.11 mg/kg/day using a default body weight of 70 kg.

[i] The EPA OW Drinking Water Criteria does not calculate a CSF but reports two CSFs from EPA (1987jj, 10532190): a CSF of 0.02 $(mg/kg/day)^{-1}$ using male mouse liver tumor data and a CSF of 0.006 $(mg/kg/day)^{-1}$ using male rat kidney tumor data.

[j] This health assessment did not designate a cancer descriptor based on EPA's cancer guidelines, but states that 1,4-dichlorobenzene is included in Group II—probably carcinogenic to humans (sufficient evidence in animals; inadequate data in humans).

[k] The WHO GDWQ does not cite NTP (1987, 2961751) directly, but rather cites WHO {1991, 81628} which identifies NTP (1987, 2961751) as the study upon which the oral RfD was based.

[l] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPP heath assessments and OPPT risk evaluations are preferred for regulated industrial chemicals such as 1,4-dichlorobenzene (p-dichlorobenzene). Although the EPA OPP RED {USEPA, 2008e, 10509481} was the most current health assessment available, it did not derive a relevant toxicity value (e.g., an oral RfD or CSF). Additionally, the OPPT risk evaluation for 1,4-dichlorobenzene (p-dichlorobenzene) is ongoing (the Final Scope of the Risk Evaluation for p-Dichlorobenzene was finalized in August of 2020) and was not selected because it was not available by the SYR 4 cut-off date of November 2020. If finalized by the SYR 5 cut-off date for identifying assessments, then it will be considered in the next SYR cycle (SYR 5).

The health assessment selected for SYR 4 is the ATSDR Toxicological Profile {ASTDR, 2006a, 5160103} (bolded in Table 6-129) because it is the most recently published health assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. The CalEPA PHG {CalEPA, 1997f, 5155646} also derived an oral CSF for 1,4-dichlorobenzene, but the critical study used to derive the oral CSF predates the available EPA health assessments and, thus, does not introduce new science and was not further considered for assessment selection.

In the ATSDR Toxicological Profile, a one-year oral bioassay {Naylor and Stout, 1996, 5017705} was chosen to derive a POD for the chronic oral RfD. In this study, groups of five male and five female beagle dogs were administered 1,4-dichlorobenzene in gelatin capsules at doses of 0, 10, 50, or 75 mg/kg/day for 5 days/week for one year. The initial high dose of 150 mg/kg/day was reduced to 75 mg/kg/day by the sixth week in both sexes due to unexpected severe toxicity; therefore, the high dose of 75 mg/kg/day is a time-weighted average. BMD analysis was conducted to derive a $BMDL_{1SD}$ of 9.97 mg/kg/day for increased serum alkaline phosphatase in female dogs. The $BMDL_{1SD}$ of 9.97 mg/kg/day was used as the POD and was duration-adjusted for the 5 day/week dosing schedule to 7 mg/kg/day. A total uncertainty factor of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF to the duration-adjusted POD, the chronic oral RfD was calculated to be 0.07 mg/kg/day.

The ATSDR Toxicological Profile does not assign a cancer descriptor to 1,4-dichlorobenzene; however, based on available evidence from animal studies, EPA concluded that 1,4-dichlorobenzene is "not likely to be carcinogenic to humans below doses that do not perturb normal liver homeostasis" {U.S. EPA, 2008e, 10509481} based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

6.2.4.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for 1,4-dichlorobenzene which was September 2019 {U.S. EPA, 2020f, 10565932}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,4-dichlorobenzene was defined as one year prior to September 2019, resulting in a search date range from September 1, 2018 to September 23, 2022.

From this literature search, 106 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In

Vitro. Five of these 106 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 101 of the 106 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-130.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,4-dichlorobenzene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-130. Evidence Stream Heat Map Results for p-dichlorobenzene (1,4-dichlorobenzene)[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	13
Environmental Fate	–	52
Human	All	41
	Epidemiologic Quantitative Analyses	5
In Vitro	–	12
No Tag	–	13
Total Unique Studies		**101**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.4.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Comparison of the potential MCLG identified in the health assessment search with the basis of the MCLG for 1,4-dichlorobenzene is shown in Table 6-131.

Table 6-131. Comparison of Existing and Potential MCLGs for 1,4-Dichlorobenzene (p-Dichlorobenzene)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1987ii, 5020212)	–	–	–	C	–	–	–	–	–	–
EPA (1987ii, 5020212)	NTP (1987, 2961751)	Liver and kidney effects in rats	–	–	0.1	20%	General Population	70 kg adult, 2 L/day	0.075[d]	–
Relevant Health Assessments Identified in SYR 4										
EPA (2008e, 10509481)	–[e]	Liver tumors in mice and renal tumors in male rats	–	L/N[f]	–	–	–	–	–	–
ATSDR (2006a, 5160103)	NTP (1987, 2961751)	Changes in ALP levels of female dogs	–	–	0.07	20%	General Population	33.8 mL/kg/ day	–	0.4

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity.

[e] Information not provided in EPA OPP, 2008.

[f] The EPA OPP, 2008 document identifies 1,4 p-dichlorobenzene as "not likely to be carcinogenic to humans below doses that do not perturb normal liver homeostasis." Therefore, the SYR 4 potential MCLG is derived using the RfD approach without an additional risk management safety factor.

6.2.4.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,4-dichlorobenzene (p-dichlorobenzene) was published on July 8, 1987 {U.S. EPA, 1987m, 3809376}. Based on an RfD of 0.1 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.075 mg/L and assigned 1,4-dichlorobenzene a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1987ii, 5020212}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986, 199530}. This MCLG was derived using the RfD from the 1987 EPA OW Health Advisory for 1,4-dichlorobenzene {U.S. EPA, 1987ii, 5020212} and applying an additional risk management safety factor of 10 to account for possible carcinogenicity {U.S. EPA, 1987m, 3809376} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor). Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the ATSDR Toxicological Profile {ATSDR, 2006a, 5160103} to derive the potential MCLG because it is the most recently published assessment that derives and oral toxicity value and used the best available science in its evaluation of non-cancer risk. Based on an RfD of 0.07 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population) {U.S. EPA, 2019, 7267482}, and an RSC of 20%, EPA calculated a potential MCLG of 0.4 mg/L. ATSDR did not assign a cancer classification to 1,4-dichlorobenzene in its profile. Based on the analysis and conclusion presented in the most recent health assessment of carcinogenic potential, the cancer classification for 1,4-dichlorobenzene was updated to "not likely to be carcinogenic to humans below doses that do not perturb normal liver homeostasis" {USEPA, 2008e, 10509481} based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. As a result of this conclusion, the risk management safety factor of 10 was removed when calculating the potential MCLG. EPA concluded that new health effects information supports raising the current MCLG of 0.075 mg/L to the potential MCLG of 0.4 mg/L.

6.2.5 1,2-Dichloroethane (1,2-DCA) (CAS# 107-06-2 | DTXSID6020438)

6.2.5.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,2-dichloroethane on July 8,1987 {U.S. EPA, 1987m, 3809376}. The NPDWR established a recommended MCLG of zero based on evidence of carcinogenicity in rodents {NCI, 1978a, 6579391} with a classification of B2 due to sufficient evidence of carcinogenicity in animals and inadequate evidence in humans {U.S. EPA, 1987m, 3809376} based on the Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1984a, 33496} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L {U.S. EPA, 1987m, 3809376}.

6.2.5.2 Results of the SYR 4 Health Assessment Search

The following table shows the final, health assessments relevant to chronic toxicity available for 1,2-dichloroethane (1,2-DCA) that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-132.

Table 6-132. Assessments Identified for 1,2-Dichloroethane (1,2-DCA)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1987a, 5113321}	–	–	–	**0.091**	**NCI (1978a, 6579391)**	**B2[d]**

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987kk, 10533341}	0.074[e]	NOAEL	Heppel et al. (1946, 62605); Spencer et al. (1951, 62617); Hofmann et al. (1971, 62606)	–	–	B2[d]
CalEPA PHG {CalEPA, 2005c, 5155608}[f]	0.0453[g]	NOAEL	NTP (1991, 1772371)	0.047[h]	NCI (1978a, 6579391)	Refer to IRIS[i]
ATSDR Toxicological Profile {ATSDR, 2001, 412348}	0.2[j]	LOAEL	NTP (1991, 1772371)	Refer to IRIS[i]	Refer to IRIS[i]	Refer to IRIS[i]
WHO GDWQ {WHO, 2003f, 6305381}	–	–	–	–	–	–
EPA ORD PPRTV {U.S. EPA, 2010m, 1258156}	0.02[k]	LOAEL	NTP (1991, 1772371)	Refer to IRIS[i]	Refer to IRIS[i]	Refer to IRIS
HC GDWQ {HC, 2014c, 7310488}	0.078	$BMDL_{10}$	NTP (1991, 1772371)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] "Probable human carcinogen," based on EPA's 1984 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1984a, 33496}.

[e] This is an inhalation total absorbed dose (TAD)/UF. The EPA OW Health Advisory assessment provides an inhalation NOAEL of 405 mg/m^3 for adverse effects in rats and guinea pigs, derived using "a combination of three inhalation studies in which various animal species were exposed to 1,2-dichloroethane for up to eight months." The TAD of 7.4 mg/kg/day was calculated using the NOAEL and applying several exposure factors (i.e., 6 hour/day, 5 day/week exposure frequency; 0.3 fraction of test substance absorbed; and 70-kg adult body weight). The UF is 100, which was "chosen in accordance with National Academy of Science/Office of Drinking Water guidelines for use with a NOAEL from an animal study." The EPA OW Health Advisory assessment did not derive a lifetime HA because there are no adequate data to do so; however, the assessment calculated a longer-term HA of 2.6 mg/L based on the TAD (adjusting for assumed daily water consumption and applying the UF of 100).

[f] The 2005 re-evaluation of the PHG for 1,2-dichloroethane is a memorandum confirming support for the 1999 PHG determination {CalEPA, 1999f, 625285}.

[g] POD/UF calculated based on a POD of 45.3 mg/kg/day and a UF of 1,000.

[h] This CSF was derived from the incidence rate of hemangiosarcoma in male rats {NCI, 1978a, 6579391} and was used by CalEPA to develop a PHG because it is based on the most sensitive species and the most sensitive tumor site.

[i] This assessment defers to the corresponding IRIS information listed above.

[j] This is an intermediate-duration oral MRL; a chronic-duration oral MRL has not been derived because an appropriate study was not identified.

[k] This value is a subchronic oral RfD. No suitable chronic data were available to derive a chronic RfD. A provisional potential chronic RfD of 0.006 mg/kg/day (based on a LOAEL of 58 mg/kg/day from NTP (1991, 1772371) and an UF of 10,000) was calculated but was included in an appendix to the EPA ORD PPRTV document because of the uncertainty associated with this derivation.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as 1,2-dichloroethane. However, the OPPT risk evaluation for 1,2-dichloroethane is ongoing (the Final Scope of the Risk Evaluation for 1,2- Dichloroethane was finalized in August of 2020) and therefore, was not selected since it was not available by the SYR 4 cut-off date of November 2020. If finalized by the SYR 5 cut-off date for identifying assessments, it will be considered in the next SYR cycle (SYR 5).

The health assessment selected for SYR 4 is the 1987 IRIS Chemical Assessment for 1,2-dichloroethane {U.S. EPA, 1987a, 5113321} (bolded in Table 6-132) because this is an EPA assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for 1,2-dichloroethane. Although there were more recent health assessments for 1,2-dichloroethane {CalEPA, 2005c, 5155608; ATSDR, 2001, 412348; WHO, 2003f, 6305381; U.S. EPA, 2010m, 1258156; HC, 2014c, 7310488}, these health assessments either did not derive a cancer slope factor or they derived a cancer slope factor based on the same critical study {NCI, 1978a, 6579391} that served as the basis for cancer slope factor derived in the selected health assessment for 1,2-dichloroethane

In 1987 IRIS Chemical Assessment for 1,2-dichloroethane, EPA selected a chronic oral study that dosed both rats and mice for 78 weeks {NCI, 1978a, 6579391}. Briefly, 1,2-dichloroethane in corn oil was administered by oral gavage to groups of Osborne-Mendel rats and B6C3F1 mice (50 animals/sex/group/species). High mortality was observed, and time-weighted average doses were reported to be 47 and 95 mg/kg/day for rats, 97 and 195 mg/kg/day for male mice, and 149 and 299 mg/kg/day for female mice. All high-dose male rats died after 23 weeks of observation, and all high-dose female rats died after 15 weeks. Tumors were induced by 1,2-dichloroethane in both sexes of both rodent species. Male rats had significantly increased incidence of forestomach squamous-cell carcinomas and circulatory system hemangiosarcomas {NCI, 1978a, 6579391}. The dose-related increased incidence of hemangiosarcoma in male rats was selected to derive the oral CSF. It was assumed that rats with hemangiosarcomas were killed by the tumors, and thus a time-to-event analysis was used to calculate the risk estimate. The 95% upper bound of the risk was calculated using 90 weeks to approximate the lifetime risk of 1,2-dichloroethane. EPA derived a CSF of 0.091 $(mg/kg/day)^{-1}$ using a linearized multistage procedure with time-to-death analysis with "extra risk" as the extrapolation method {U.S. EPA, 1987a, 5113321}.

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, 1,2-dichloroethane is classified as a Group B2 "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 {U.S. EPA, 1987a, 5113321}. Because dichloroethane is classified as a "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.5.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for 1,2-Dichloroethane which was September 2019 {U.S. EPA, 2020e, 10617338}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,2-Dichloroethane was defined as one year prior to September 2019 resulting in a search date range from September 1, 2018 to September 27, 2022.

From this literature search, 522 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Six of these 522 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 516 of the 522 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-133.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,2-dichloroethane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-133. Evidence Stream Heat Map Results for 1,2-Dichloroethane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	94
Environmental Fate	–	121
Human	All	377
	Epidemiologic Quantitative Analyses	25
In Vitro	–	152
No Tag	–	16
Total Unique Studies		**516**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.5.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-134 shows the comparison of the basis for the existing and potential MCLGs for 1,2-dichloroethane (1,2-DCA).

Table 6-134. Comparison of of the Basis for the Existing and Potential MCLGs for 1,2-Dichloroethane (1,2-DCA)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987m, 3809376)	NCI (1978a, 6579391)	Hemangiosarcomas	0.091	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (1987a, 5113321)	NCI (1978a, 6579391)	Hemangiosarcomas	0.091	B2	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.5.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,2-dichloroethane (1,2-DCA) was published on July 7, 1987 { U.S. EPA, 1987m, 3809376}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1985d, 3809374}, according to EPA's 1984 Proposed Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1984a, 33496}, EPA set the MCLG at zero {U.S. EPA, 1985d, 3809374}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 1987 IRIS Chemical Assessment for 1,2-dichloroethane {U.S. EPA, 1987a, 5113321}, the same assessment that the current NPWDR is based on, to derive the potential MCLG because it used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for 1,2-dichloroethane. Furthermore, other available health assessments either did not derive a cancer slope factor or they derived a cancer slope factor based on the same critical study. There was no update to the cancer descriptor in the selected health assessment, thus the cancer classification was maintained at B2, "probable human carcinogen," in accordance with the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. For 1,2-DCA, more recent information does not support a change to the MCLG.

6.2.6 trans-1,2-Dichloroethylene (CAS# 156-60-5 | DTXSID7024031)

6.2.6.1 Basis of the Existing MCLG

EPA published the current NPDWR for trans-1,2-dichloroethylene on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established both an MCLG and an MCL of 0.1 mg/L. EPA based the MCLG on a reference dose of 0.02 mg/kg/day {U.S. EPA, 1990c, 1739793} and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991a, 5499} in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.2.6.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for trans-1,2-dichloroethylene that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-135.

Table 6-135. Assessments Identified for trans-1,2-Dichloroethylene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987ll, 9109789}	0.01[d]	LOAEL	Quast et al. (1983, 64323)	–	–	D[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990c, 1739793}	0.02	NOAEL	Barnes et al. (1985, 200220)	–	–	–[f]
ATSDR Toxicological Profile {ATSDR, 1996, 723873}	0.2[g]	NOAEL	Barnes et al. (1985, 200220)	–	–	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2003f, 6305381}	0.017	NOAEL	Barnes et al. (1985, 200220)	–	–	–
EPA IRIS Chemical Assessment {U.S. EPA, 2010h, 5185076}	**0.02**	**$BMDL_{1SD}$**	**Shopp et al. (1985, 5435222)**	–	–	I[h]
CalEPA PHG {CalEPA, 2018a, 10489860}	0.0048	$BMDL_{1SD}$	Shopp et al. (1985, 5435222)	–	–	–
EPA ORD PPRTV {U.S. EPA, 2020g, 10533336}	Refer to IRIS[i]	–	–	–	–	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; BMDL = benchmark dose level; $BMDL_{1SD}$ = lower 95% confidence limit on the benchmark response of 1 standard deviation change in the control mean.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), acceptable daily dose (ADD), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Data from a chronic drinking water study in rats exposed to 1,1-dichloroethylene was used to derive this RfD.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] The health assessment states, "There are no data available which describe the carcinogenic potential of cis or trans-1,2-DCE."

[g] This health assessment derived an intermediate-duration oral exposure MRL. No chronic MRL was derived because no human or animal data were located regarding health effects of chronic exposure to 1,2-dichloroethylene.

[h] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[i] This health assessment defers to the EPA IRIS Chemical Assessment for trans-1,2-dichloroethylene {U.S. EPA, 2010h, 5185076}.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as trans-1,2-dichloroethylene. However, the OPPT risk evaluation for trans-1,2-dichloroethylene is ongoing (the Final Scope of the Risk Evaluation for 1,2- Dichloroethylene was finalized in August of 2020) and was not selected because it was not available by the SYR 4 cut-off date of November 2020. If the OPPT assessment is finalized by the SYR 5 cut-off date for identifying assessments, it will be considered in the next SYR cycle (SYR 5).

The health assessment selected for SYR 4 is the EPA IRIS Chemical Assessment {U.S. EPA, 2010h, 5185076} (bolded in Table 6-135) because it is an EPA assessment that derives an oral toxicity value and used the best available science in its evaluation of non-cancer risk. Although more current health assessments were available, the CalEPA PHG {CalEPA, 2018a, 10489860} was based on the same critical study and modeling approach as the selected IRIS assessment, and the PPRTV assessment {U.S. EPA, 2020g, 10533336} referenced the toxicity value derived by the IRIS assessment {U.S. EPA, 2010h, 5185076}.

In the 2010 IRIS health assessment, a 90-day subchronic study evaluated the effects of trans-1,2-dichloroethylene in drinking water in CD-1 mice {Shopp et al. 1985, 5435222}. Mice (10/sex/dose) were exposed to drinking water with 0.1, 1.0, or 2.0 mg/mL for 90 days. Exposed male mice showed a decrease in humoral immune response at all dose levels, as measured by decrease in the number of antibody-

forming cells (AFCs) in the spleen against sheep red blood cells (sRBCs) {Shopp, 1985, 5435222}. EPA considered this effect to be biologically significant and used the decrease in AFC number in male mice as the critical effect for the basis for BMD modeling. EPA used these 90-day subchronic oral toxicity test values to derive the $BMDL_{1SD}$ of 65 mg/kg/day, a value that represents the 95% lower confidence limit on the benchmark dose corresponding to a change in the mean response equal to 1 standard deviation from the control mean number of AFCs (equivalent to an approximately 20% decrease in AFCs per 10^6 spleen cells). This $BMDL_{1SD}$ of 65 mg/kg/day was selected as the POD for trans-1,2-dichloroethylene. A total uncertainty factor (UF) of 3,000 was applied to the POD: 10 for interspecies variability, 10 for intraspecies variability, 10 for extrapolation from subchronic to chronic exposure, and 3 for database deficiencies due to lack of reproductive toxicity data. After applying the total UF to the POD, the chronic oral RfD was calculated to be 0.02 mg/kg/day.

EPA concluded that there is "inadequate information to assess the carcinogenic potential" of trans-1,2-dichloroethylene and classified it as "Group I" {U.S. EPA, 2010h, 5185076}, according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. This determination was based on the absence of epidemiological studies in humans and lack of animal studies designed to evaluate its carcinogenic potential.

6.2.6.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for trans-1,2-dichloroethylene which was July 2019 {U.S. EPA, 2020h, 10565934}.The start date of the SYR 4 literature search conducted in PubMed and Web of Science for trans-1,2-dichloroethylene was defined as one year prior to July 2019 resulting in a search date range from July 1, 2018 to September 29, 2022.

From this literature search, 13 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Following SWIFT-Review, all 13 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-136.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,2-dichloroethylene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-136. Evidence Stream Heat Map Results for trans-1,2-Dichloroethylene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	5
Environmental Fate	–	8
Human	All	5
	Epidemiologic Quantitative Analyses	0
In Vitro	–	6
No Tag	–	0

Tag	Sub Tag	Number of Studies
Total Unique Studies		**13**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.6.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Comparison of the PODs identified in the health assessment search with the basis of the MCLG is shown in Table 6-137.

Table 6-137. Comparison of the Basis for the Existing and Potential MCLGs for trans-1,2-Dichloroethylene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA, (1991a, 5499)	–	–	–	D	–	–	–	–	–	–
EPA{1990c, 1739793}	Barnes et al., (1985, 200220)	Males: increases in serum alkaline phosphatase Females: decreases in relative thymus weight	–	–	0.02	20%	General Population	70 kg adult, 2 L/day	0.1	–
Relevant Health Assessment Identified in SYR 4										
EPA (2010h, 5185076)	–	–	–	I	–	–	–	–	–	–
EPA (2010h, 5185076)	Shopp et al., (1985, 5435222)	Decrease in number of antibody-forming cells (AFCs) against sheep red blood cells (sRBCs) in male mice	–	–	0.02	20%	General Population	33.8 mL/kg/ day	–	0.1

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.6.5 SYR 4 Health Effects Conclusion

The existing NPDWR for trans-1,2-dichloroethylene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.02 mg/kg/day {U.S. EPA, 1990c, 1739793}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.1 mg/L and assigned trans-1,2-dichloroethylene a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1991a, 5499}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment {U.S. EPA, 2010h, 5185076} to derive the potential MCLG because it is an EPA health assessment that derives and oral toxicity value and used the best available science in its evaluation of non-cancer risk. Although more current health assessments were available, the CalEPA PHG {CalEPA, 2018a, 10489860}, was based on the same critical study and modeling approach as the selected IRIS chemical assessment and the PPRTV health assessment {U.S. EPA, 2020g, 10533336} referenced the toxicity value derived by the selected IRIS assessment {U.S. EPA, 2010h, 5185076}. Based on an RfD of 0.02 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.1 mg/L. Based on the analysis and conclusion presented in this health assessment, the cancer classification was updated to I, "inadequate information to assess carcinogenic potential," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that, based on the available health effects information, there is no potential to change the existing MCLG of 0.1 mg/L.

6.2.7 Dichloromethane (CAS# 75-09-2 | DTXSID0020868)

6.2.7.1 Basis of the Existing MCLG

EPA published the current NPDWR for dichloromethane on July 17, 1992 {U.S. EPA, 1992g, 10587719}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1992m, 2531041} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L, based on the practical quantitation limit for dichloromethane at the time {U.S. EPA, 1992g, 10587719}.

6.2.7.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for dichloromethane that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-138.

Table 6-138. Assessments Identified for Dichloromethane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987mm, 10719816}	0.05	NOAEL	Hazleton Laboratories (1982, 10709973)	–	–	B2[d]
EPA OW Final Quantification of Toxicological Effects {U.S. EPA, 1992m, 2531041}	0.05	NOAEL	Serota et al. (1986a, 730592)	–	–	B2[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1993d, 10492399}	0.06	NOAEL	Serota et al. (1986a, 730592)	–	–	B[d]
ATSDR Toxicological Profile {ATSDR, 2000, 192113}	0.06	NOAEL	Serota et al. (1986a, 730592)	–	–	Refer to IRIS
CalEPA PHG {CalEPA, 2000c, 3982295}	0.06[e]	NOAEL	Serota et al. (1986a, 730592)	0.004[f]	Serota et al. (1986a, 730592)	Refer to IRIS
WHO GDWQ {WHO, 2003o, 10509430}	0.006	NOAEL	Serota et al. (1986a, 730592)	–	–	–
HC GDWQ {HC, 2011, 10528737}	0.014	$BMDL_{10}$	Serota et al. (1986a, 730592)	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2011c, 808655}	0.006	$BMDL_{10}$	Serota et al. (1986a, 730592)	**0.002**	**Serota et al. (1986a, 730592); Hazleton Laboratories (1983, 29131)**	**L[g]**
EPA OPPT Risk Evaluation {U.S. EPA, 2020i, 6811894}	Refer to IRIS	–	–	–	–	L[g]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] POD/UF calculated based on a POD of 6 mg/kg/day and a UF of 100.

[f] The CalEPA PHG document reported multiple oral CSFs derived using different modeling parameters. The CSF reported here is the one used by CalEPA to derive the PHG.

[g] "Likely to be carcinogenic to humans" based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

Following the decision logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as dichloromethane. The OPPT Risk Evaluation for Dichloromethane was considered during SYR 4 because it was finalized by the SYR 4 cut-off date, in November 2020 {U.S. EPA, 2020i, 6811894}. However, the health assessment selected for SYR 4 is the 2011 IRIS Toxicological Review of Dichloromethane (Methylene Chloride) {U.S. EPA, 2011c, 808655} (bolded in Table 6-44) since it was the most recently published health assessment that derives an oral toxicity value and used the best available science in its evaluation of cancer risk and derivation of cancer slope factor. Although the 2020 OPPT Risk Evaluation is a more recent health assessment for dichloromethane, it did not derive an oral CSF {U.S. EPA, 2020i, 6811894}.

In the 2011 IRIS Toxicological Review for Dichloromethane, EPA selected a two-year mouse drinking water study {Hazleton Laboratories, 1983, 29131; Serota, 1986b, 730593} as the critical study to derive an oral slope factor. In this study, male and female B6C3F1 mice were exposed to dichloromethane in drinking water (target doses of 0, 60, 125, 185, or 250 mg/kg/day) for 104 weeks. There was a statistically significant dose-response of increasing liver tumor incidence with increasing dose in male mice (hepatocellular adenoma and carcinoma). An oral slope factor of 2×10^{-3} $(mg/kg/day)^{-1}$ (rounded from 1.7×10^{-3}) was derived from the male mouse liver tumor response study reported in both Serota et al. (1986b, 730593) and Hazleton Laboratories (1983, 29131). The oral slope factor was derived using a physiologically-based pharmacokinetic (PBPK) model based on liver internal doses in B6C3F1 mice that were allometrically scaled based on a tissue-specific glutathione S-transferase (GST)-mediated metabolism dose metric for the population with the presumed highest greatest sensitivity to carcinogenic effects of dichloromethane: individuals with the GST-T1 homozygous positive ($^{+/+}$) genotype (wild type, representing approximately 30% of the human population). Because dichloromethane metabolism via GST-T1 results in the formation of a reactive metabolite that damages DNA and results in the formation of tumors, individuals with the greater GST-T1 activity are expected to be at increased carcinogenic risk related to dichloromethane exposure.

Based on the available information and following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA determined that dichloromethane is "likely to be carcinogenic in humans" {U.S. EPA, 2011c, 808655}. This classification is based on evidence of carcinogenicity in a two-year inhalation exposure study that demonstrated liver and lung tumors in B6C3F1 mice {NTP, 1986b, 29242}, and the two-year drinking water exposure study described above that resulted in liver tumors in male B6C3F1 mice {Serota, 1986b, 730593; Hazleton Laboratories, 1983, 29131}. Because dichloromethane is classified as "likely to be carcinogenic in humans," the available noncancer toxicity values were not evaluated for potential MCLG derivation.

6.2.7.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT within the Office of Chemical Safety and Pollution Prevention (OCSPP) conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. From the SYR 4 health assessment search, the EPA OPPT Risk Evaluation for Methylene Chloride (Dichloromethane, DCM) was the most recent health assessment, and was therefore used to assign the date limit {U.S. EPA, 2020i, 6811894}. Since the OPPT Risk Evaluation for Methylene Chloride (Dichloromethane, DCM) conducted a literature search through March 2017 {U.S. EPA, 2020i, 6811894}, the start date of the SYR 4 literature search conducted in PubMed and Web of Science for dichloromethane was defined as one year prior to March 2017, resulting in search date range from March 1, 2016 to January 27, 2022.

From this literature search, 1,035 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Sixty of these 1,035 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 975 of the 1,035 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-139.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for dichloromethane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-139. Evidence Stream Heat Map Results for Dichloromethane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	359
Environmental Fate	–	259
Human	All	456
	Epidemiologic Quantitative Analyses	31
In Vitro	–	506
No Tag	–	86
Total Unique Studies		**975**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.7.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-140 shows the comparison of the basis for the existing and potential MCLGs for dichloromethane.

Table 6-140. Comparison of Existing and Potential MCLGs for Dichloromethane

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1992m, 2531041)	Serota et al. (1986b, 730593; 1986a, 730592)	–	–	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2011c, 808655)	Serota et al. (1986a, 730592); Hazleton Laboratories, (1983, 29131)	Hepatocellular adenoma and carcinoma	0.002	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed as mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.7.5 SYR 4 Health Assessment Conclusion

The existing NPDWR for dichloromethane was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1992m, 2531041}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2011 EPA IRIS Toxicological Review of Dichloromethane (Methylene Chloride) {U.S, EPA, 2011c, 808655} because it was the most recently published health assessment that derives an oral toxicity value and uses the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. Based on the analysis and conclusion presented in this health assessment, a CSF of 0.002 $(mg/kg/day)^{-1}$ was derived and the cancer descriptor was updated to L, "likely to be carcinogenic to humans," according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For dichloromethane, the more recent cancer descriptor of L, "likely to be carcinogenic to humans," would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.2.8 1,2-Dichloropropane (CAS# 78-87-5 | DTXSID0020448)

6.2.8.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,2-dichloropropane on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1990g, 2799416} according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L based on the practical quantitation limit.

6.2.8.2 Results of the SYR 4 Health Assessment Search

The following table shows the final health assessments relevant to chronic toxicity available for 1,2-dichloropropane that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-141.

Table 6-141. Assessments Identified for 1,2-Dichloropropane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	–	–	–	0.0633	NTP (1983, 10489887)	C[d]
ATSDR Toxicological Profile {ATSDR, 1989a, 5160134}	0.09	LOAEL	NTP (1986c, 67963)	–	–	–
EPA OW Drinking Water Criteria Document {U.S. EPA, 1990g, 2799416}	–	–	–	0.067	NTP (1986c, 67963)	B2[d]

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment Summary {U.S. EPA, 1991n, 7681886}[e]	–	–	–	–	–	–
CalEPA PHG {CalEPA, 1999g, 5155640}	0.0893[f]	LOAEL	NTP (1986c, 67963)	0.036	NTP (1986c, 67963)	–
WHO GDWQ {WHO, 2003p, 10661784}	0.014	LOAEL	Bruckner et al. (1989, 67910)	–	–	–
EPA ORD PPRTV {U.S. EPA, 2016d, 6571209}	0.04	$BMDL_{05}$	Kirk et al. (1995, 688858)	**0.037**	**NTP (1986c, 67963)**	**L[g]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level; $BMDL_{05}$ = benchmark dose level at the 95% lower confidence limit on a 5% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] An inhalation RfC was derived in this 1991 health assessment {U.S. EPA, 1991n, 7681886} but an oral RfD was not derived and a cancer assessment was not performed.

[f] This is a POD/UF. CalEPA did not derive this oral reference value in its health assessment but specified a POD of 89.3 mg/kg/day and a UF of 1,000.

[g] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), EPA OPPT risk evaluations are preferred for regulated industrial chemicals such as 1,2-dichloropropane. However, an EPA OPPT risk evaluation for 1,2-dichloropropane was not available by the SYR 4 health assessment search cut-off date of November 2020. An EPA OPPT risk evaluation for 1,2-dichloropropane is ongoing (the Final Scope of the Risk Evaluation for 1,2-Dichloroproane was finalized in August of 2020) and if finalized by the SYR 5 cut-off date for identifying health assessments, it will be considered in the next SYR cycle (SYR 5).

The health assessment selected for SYR 4 is the 2016 EPA ORD PPRTV {U.S. EPA, 2016d, 6571209} (bolded in Table 6-141) because this is the most recently published EPA health assessment that derives an oral toxicity value and it used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for 1,2-dichloropropane. In the 2016 EPA ORD PPRTV, EPA selected an NTP two-year bioassay in rats and mice {NTP, 1986c, 67963} as the critical study to develop a provisional oral slope factor (p-OSF). Groups of 50 male and female B6C3F1 mice and female F344/N rats were administered 1,2-dichloropropane in corn oil via gavage at doses of 0, 125, or 250 mg/kg/day five days a week for 103 weeks. Male F344/N rats received 0, 62, or 125 mg/kg/day on the same schedule. An increased incidence of combined hepatocellular adenoma and carcinoma of the liver was observed in all exposed groups of male and female mice. Doses were converted to HEDs using $(body\ weight)^{3/4}$ scaling and BMD modeling was performed to determine $BMDL_{10[HED]}$s. The increased incidence of hepatocellular adenomas and carcinomas in male mice was identified as the critical effect because it resulted in the lowest $BMDL_{10[HED]}$ (2.71 mg/kg/day) compared to other candidate endpoints from the

critical study. The $BMDL_{10[HED]}$ of 2.71 mg/kg/day for this effect in male mice was the POD that EPA used to derive the p-OSF of 0.037 $(mg/kg/day)^{-1}$ based on a 10% excess cancer risk.

Following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA has described 1,2-dichloropropane as "likely to be carcinogenic to humans," which corresponds to a cancer classification of L based on the available animal data and data on carcinogenic effects in humans {U.S. EPA, 2016e, 5113352}. Because 1,2-dichloropropane is classified as "likely to be carcinogenic to humans," the available noncancer toxicity values were not evaluated for potential MCLG derivation.

6.2.8.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date of September 2009 indicated in the OPPT Final Scope of the Risk Evaluation for 1,2-dichloropropane {U.S. EPA, 2020j, 10565937}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,2-dichloropropane was defined as one year prior to September 2019, resulting in a search date range from September 1, 2018 to September 28, 2022.

From this literature search, 31 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. One of these 31 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 30 of the 31 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-142.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for 1,2-dichloropropane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-142. Evidence Stream Heat Map Results for 1,2-Dichloropropane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	6
Environmental Fate	–	10
Human	All	22
	Epidemiologic Quantitative Analyses	9
In Vitro	–	4
No Tag	–	2
Total Unique Studies		**30**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.8.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-143 shows the comparison of the basis for the existing and potential MCLGs for 1,2-dichloropropane.

Table 6-143. Comparison of the Basis for Existing and Potential MCLGs for 1,2-Dichloropropane

Reference	Critical Study	Critical Effect	Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1990g, 2799416)	NTP (1986c, 67963)	Hepatocellular adenoma and carcinoma in male mice	0.067	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2016d, 6571209)	NTP (1986c, 67963)	Hepatocellular adenoma and carcinoma in male mice	0.037	L	–	–	–	0

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.8.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,2-dichloropropane was published on January 30, 1991 {U.S. EPA 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1990g, 2799416} according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the 2016 U.S. EPA ORD PPRTV {U.S. EPA, 2016d, 6571209} to derive the potential MCLG because this is the most recently published EPA health assessment that derives an oral toxicity value and used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor. Based on the analysis and conclusion presented in the 2016 U.S. EPA ORD PPRTV and following EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, the cancer classification for 1,2-dichloropropane was changed to "likely to be carcinogenic to humans." The existing MCLG of zero provides the maximum health protection; therefore, EPA concluded that the MCLG remains health protective. For 1,2-dichloropropane, EPA concluded that the MCLG remains health protective. For 1,2-dichloropropane, the more recent cancer descriptor of L, "likely to be carcinogenic to humans," would also lead to an MCLG of zero; therefore, the more recent information does not support a change to the MCLG.

6.2.9 Di(2-ethylhexyl)phthalate (CAS# 117-81-7 | DTXSID5020607)

6.2.9.1 Basis of the Existing MCLG

EPA published the current NPDWR for DEHP on July 17, 1992 {U.S. EPA, 1992n, 10529459). The NPDWR established an MCLG of zero and a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1988b, 5113322} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR established an MCL of 0.006 mg/L, based on the Practical Quantitation Limit (PQL) and limited by analytical feasibility {U.S. EPA, 1992n, 10529459).

6.2.9.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for di(2-ethylhexyl)phthalate that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-144.

Table 6-144. Assessments Identified for Di(2-ethylhexyl)phthalate

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1988b, 5113322}[d]	0.02	LOAEL	Carpenter et al. (1953, 63433)	**0.014**	**NTP (1982c, 5160110)**	**B2[e]**
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992n, 10529459}	0.02	LOAEL	Carpenter et al. (1953, 63433)	0.014	NTP (1982c, 5160110)	Refer to IRIS[f]
CalEPA PHG {CalEPA, 1997g, 5155636}	0.0142[g]	NOAEL	NTP (1984, 10489885)	0.003	Corning (1996, 10366163)	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile {ATSDR, 2002c, 679117}	0.06	NOAEL	David et al. (2000, 673620)	–	–	Refer to IRIS[f]
WHO GDWQ {WHO, 2003q, 5926021}	0.025[h]	NOAEL	Morton (1979, 10519846)	–	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.
[a] Selected health assessment and chronic toxicity value bolded.
[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).
[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified
[d] Oral RfD last revised in 1987 {U.S. EPA, 1988b, 5113322}; carcinogenicity assessment last revised in 1988 {U.S. EPA, 1988b, 5113322}.
[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.
[f] This assessment defers to the corresponding IRIS information listed above.
[g] POD/UF based on a POD of 14.2 mg/kg/day and a UF of 1,000.
[h] TDI derived using POD from subchronic (7-day) oral study.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as di(2-ethylhexyl)phthalate. However, the OPPT risk evaluation for di(2-ethylhexyl)phthalate is ongoing (the Final Scope of the Risk Evaluation for Di(2-ethylhexyl)phthalate was finalized in August of 2020) and therefore, was not available by the cut-off date of November 2020. If the OPPT risk evaluation is finalized by the cut-off date for identifying assessments in the next SYR cycle (SYR 5), it will be considered.

The health assessment selected for SYR 4 is the 1988 IRIS Toxicological Review of Di(2-ethylhexyl)phthalate (DEHP) {U.S. EPA, 1988b, 5113322} (bolded in Table 6-144) because this is an EPA health assessment that derives an oral toxicity value and used the best available science to derive the most health protective cancer slope factor for DEHP. Although more current health assessments were available, the IRIS Toxicological Review derives a more health protective CSF than CalEPA (1997g, 5155636). In addition, the ATSDR Toxicological Profile {ATSDR, 2002, 679117} and WHO GDWQ {WHO, 2003q, 5926021} did not derive an oral CSF, and the EPA OW Drinking Water Criteria Document {U.S. EPA, 1992n, 10529459} was based on the same oral CSF as the selected 1988 IRIS Toxicological Review {U.S. EPA, 1988b, 5113322}.

In the selected health assessment, EPA selected a two-year chronic cancer bioassay in B6C3F1 mice {NTP, 1982c, 5160110} for dose-response analysis and linear extrapolation of cancer risk. Animals (50/sex/dose) were exposed to 0, 3,000, or 6,000 ppm DEHP in the diet for two years. In the NTP study, powdered rodent meal was provided in such a way that measured food consumption could include significant waste and spillage rather than true food intake. For this reason, a standard food consumption rate of 13% mouse body weight was used in the dose conversion. These doses were estimated to be 0, 390, and 780 mg/kg/day DEHP, respectively {NTP, 1982c, 5160110}. NTP (1982c, 5160110) found a dose-dependent increase in hepatocellular carcinomas and adenomas in mice of both sexes, but male mice were more sensitive. Rats were also included in the NTP cancer bioassay and increased liver tumors were observed in females, but the rat data were not used for the EPA CSF derivation. EPA applied a low-dose linear extrapolation procedure to the male mouse hepatocellular carcinoma data to derive an oral CSF of 0.014 mg/kg/day for DEHP {U.S. EPA, 1988b, 5113322}.

In the selected assessment, EPA classified DEHP as Group B2, "probable human carcinogen," following the 1986 Carcinogen Risk Assessment Guidelines {U.S. EPA, 1986a, 199530}, based on supporting evidence from animal studies. Because DEHP is classified as a Group B2, "probable human carcinogen," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.9.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for di(2-ethylhexyl)phthalate which was September 2019 {U.S. EPA, 2020k, 10565938}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for di(2-ethylhexyl)phthalate was defined as one year prior to September 2019 resulting in a search date range from September 1, 2018 to September 28, 2022.

From this literature search, 1,556 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty-nine of these 1,556 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,527 of the 1,556 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-145.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for di(2-ethylhexyl)phthalate and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-145. Evidence Stream Heat Map Results for Di(2-ethylhexyl)phthalate[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	592
Environmental Fate	–	366
Human	All	1,061
	Epidemiologic Quantitative Analyses	31
In Vitro	–	516
No Tag	–	43
Total Unique Studies		**1,527**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.9.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Comparison of the potential MCLG identified in the health assessment search with the basis of the MCLG is shown in Table 6-146.

Table 6-146. Comparison of Existing and Potential MCLGs for Di(2-ethylhexyl)phthalate

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1988b, 5113322)	NTP (1982c, 5160110)	Dose-related increase in liver tumor responses in rats and mice of both sexes	0.014	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (1998b, 5113322)	NTP (1982c, 5160110)	Dose-related increase in liver tumor responses in rats and mice of both sexes	0.014	B2	–	–	–	0

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.9.5 SYR 4 Health Effects Conclusion

The existing NPDWR for di(2-ethylhexyl)phthalate was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1988b, 5113322}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the SYR 4 health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the IRIS Toxicological Review of Di(2-ethylhexyl) phthalate (DEHP) {U.S. EPA, 1988b, 5113322} because it derives an oral toxicity value and used the best available science to derive the most health protective cancer slope factor for DEHP. Based on the analysis and conclusion presented in this health assessment, the cancer classification was maintained at B2, "probable human carcinogen," according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. For di(2-ethylhexyl)phthalate, more recent information does not support a change to the MCLG.

6.2.10 Ethylene dibromide (CAS# 106-93-4 | DTXSID3020415)

6.2.10.1 Basis of the Existing MCLG

EPA published the current NPDWR for ethylene dibromide on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established a recommended MCLG of zero based on evidence of carcinogenicity in rodents {NCI, 1978b, 18160} with a cancer classification of B2 {U.S. EPA, 1987nn, 9193}, probable human carcinogen according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.00005 mg/L, based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.2.10.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for ethylene dibromide that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-147.

Table 6-147. Assessments Identified for Ethylene Dibromide

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1987nn, 9193}	–	–	–	85	NCI (1978b, 18160)	B2[d]
EPA OW Health Advisory {U.S. EPA, 1987l, 10509768}	–	–	–	–	–	B2[d]
CalEPA PHG {CalEPA, 2003g, 5155639}	0.0025[e]	NOAEL	Nitschke et al. (1981, 5598065)	3.6[f]	NCI (1978b, 18160)	B2[d]
EPA IRIS Chemical Assessment {U.S. EPA, 2004b, 594429}	0.009	LOAEL	NCI (1978, 18160)	**2**	**NCI (1978b, 18160)**	**L[g]**

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2004n, 10509439}	–	–	–	–	–	–
ATSDR Toxicological Profile {ATSDR, 2018c, 5348438}	–[h]	–	–	-	-	-

Note: POD = point of departure; RfV = reference value; CSF = cancer slope factor; dash (–) = not provided; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[e] POD/UF was calculated by EPA based on a POD of 2.49 mg/kg/day (NOAEL from a subchronic inhalation study in rats) and a UF of 1,000. The assessment reports that the subchronic inhalation study was used instead of an available chronic rat study because the former derived a NOAEL.

[f] CalEPA (1988, 10520774) was cited for this value. This value is based on results of the NCI (1978b, 18160) study and represents a geometric mean of four values (male and female mice, male and female rats).

[g] Based on a 1999 draft version of EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}.

[h] The ATSDR toxicological profile indicates that there are insufficient data for derivation of a chronic-duration oral MRL and that "excessive treatment-related mortality" was observed in the only available chronic oral study.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT assessments are preferred for regulated industrial chemicals such as ethylene dibromide. However, the OPPT risk evaluation for ethylene dibromide is ongoing (the Final Scope of the Risk Evaluation for Ethylene Dibromide was finalized in August of 2020) and was not available by the cut-off date of November 2020. If the OPPT assessment is finalized by the cut-off date for identifying assessments in the next SYR cycle (SYR 5), it will be considered.

The assessment selected for SYR 4 is the 2004 IRIS Chemical Assessment {U.S. EPA, 2004b, 594429} (bolded in Table 6-147) because this is the most recently published EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for ethylene dibromide. Though there were more recent health assessments available {WHO, 2004n, 10509439; ATSDR, 2018c, 5348438}, they did not derive a cancer slope factor for ethylene dibromide.

In the 2004 EPA health assessment, EPA selected a 2-year cancer bioassay by the National Cancer Institute {NCI, 1978b, 18160} as the critical study. In this study, 50 Osborne-Mendel rats/sex/group were administered ethylene dibromide (also known as 1,2-dibromoethane) in corn oil via oral gavage. The initial doses of 40 and 80 mg/kg/day were adjusted due to high exposure-related mortality in the high dose group. The adjusted time-weighted average low and high doses were 38 and 41 mg/kg/day for male rats, and 37 and 39 mg/kg/day for female rats. The high mortality observed in rats necessitated early termination of the study before the full 104 weeks, and male and female rats were sacrificed at 38 and 61 weeks, respectively. In this bioassay, B6C3F1 mice were also dosed and were similarly affected by high mortality, leading to early study termination.

This bioassay found that ethylene dibromide was carcinogenic to both Osborne-Mendel rats and B6C3F1 mice {NCI, 1978b, 18160}. EPA derived the CSF of 2 $(mg/kg/day)^{-1}$ for ethylene dibromide, based upon human equivalent dose estimates calculated from adjusted incidences for tumors of the forestomach,

thyroid follicular cells, and hemangiosarcomas in male rats using BMD modeling. This value represents the 95% upper bound of the confidence interval of the central tendency estimate of 1 $(mg/kg/day)^{-1}$ {U.S. EPA, 2004b, 594429}.

Ethylene dibromide has been studied for mutagenic potential in a variety of *in vivo* and *in vitro* systems and results indicate that it is a direct-acting mutagen in bacteria. Under the 1999 Draft Revised Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}, ethylene dibromide is considered "likely to be carcinogenic to humans" based on strong evidence of carcinogenicity in animals and inconclusive evidence of carcinogenicity in an exposed human population {U.S. EPA, 2004b, 594429}. This corresponds to the cancer classification of L based on the 2005 EPA Cancer Guidelines (2005d, 10263976). Because ethylene dibromide is classified as "likely to be carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.10.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for ethylene dibromide which was September 2019 {U.S. EPA, 2020j, 10565937}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for ethylene dibromide was defined as one year prior to September 2019 resulting in a search date range from September 1, 2018 to September 9, 2022.

From this literature search, 58 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Three of these 58 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 55 of the 58 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-148.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for ethylene dibromide and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-148. Evidence Stream Heat Map Results for Ethylene Dibromide[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	22
Environmental Fate	–	13
Human	All	39
	Epidemiologic Quantitative Analyses	4
In Vitro	–	22
No Tag	–	2
Total Unique Studies		**55**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.10.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-149 shows the comparison of the basis for the existing and potential MCLGs for ethylene dibromide.

Table 6-149. Comparison of the Basis for the Existing and Potential MCLGs for Ethylene Dibromide

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987nn, 9193)	NCI (1978b, 18160)	High incidence of forestomach carcinoma observed in rats	85	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2004b, 594429)	NCI (1978b, 18160)	Forestomach tumors, hemangiosarcomas, thyroid follicular cell adenomas or carcinomas in rats	2	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.10.5 SYR 4 Health Effects Conclusion

The existing NPDWR for ethylene dibromide was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on a cancer classification of B2, "probable human carcinogen," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA set the MCLG at zero. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Chemical Assessment {U.S. EPA, 2004b, 594429} because this is the most recently published EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for ethylene dibromide. Based on the analysis and conclusion presented in this health assessment, the CSF was set at 2 $(mg/kg/day)^{-1}$ and the cancer classification was updated to L, "likely to be carcinogenic to humans," according to the 1999 draft version of EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1999c, 41631}. For ethylene dibromide, the more recent cancer descriptor of L, "likely to be carcinogenic to humans," would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.2.11 Tetrachloroethylene (CAS# 127-18-4 | DTXSID2021319)

6.2.11.1 Basis of the Existing MCLG

EPA published the current NPDWR for tetrachloroethylene on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established a recommended MCLG of zero based on "strong evidence of carcinogenicity from ingestion based on consideration of the weight of evidence, pharmacokinetics and exposure" (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L based on the PQL {U.S. EPA, 1991a, 5499}.

6.2.11.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final health assessments relevant to chronic toxicity available for tetrachloroethylene (or perchloroethylene, PCE, or PERC) that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-150.

Table 6-150. Assessments Identified for Tetrachloroethylene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Health Advisory {U.S. EPA, 1987oo, 10510376}	0.0143	NOAEL	Buben and O'Flaherty (1985, 65239)	–	–	–
EPA OW Quantification of Toxicological Effects {U.S. EPA, 1990h, 10492391}	0.0143	NOAEL	Buben and O'Flaherty (1985, 65239)	–	–	–
CalEPA PHG {CalEPA, 2001b, 630408}	0.032[d]	LOAEL	Altmann et al. (1995, 195935); Spinatonda et al. (1997, 630994); Ferroni et al. (1992, 66305)	0.54	NCI (1977d, 58266)	–

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
WHO GDWQ {WHO, 2003r, 10509436}	0.014	NOAEL	Buben and O'Flaherty (1985, 65239); Hayes et al. (1986, 630606)	–	–	–
EPA IRIS Toxicological Review {U.S. EPA, 2012b, 2826528}	0.006[e]	LOAEL	Cavalleri et al. (1994, 195942); Echeverria et al. (1995, 195893)	**0.0021**	**JISA (1993, 630653)**	**L[f]**
MassDEP Assessment {MassDEP, 2014, 10571053}	–	–	–	0.02	JISA (1993, 630653)	–
HC GDWQ {HC, 2014a, 3049488}	0.0068	$BMDL_{10}$	NTP (1986d, 2951722)	–	–	–
ATSDR Toxicological Profile {ATSDR, 2019b, 5425314}	0.008[g]	LOAEL	Cavalleri et al. (1994, 195942)	Refer to IRIS[h]	Refer to IRIS	Refer to IRIS
EPA OCSPP Risk Evaluation {U.S. EPA, 2020l, 7697272}	–	–	–	Refer to IRIS	Refer to IRIS	Refer to IRIS

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided; LOAEL = lowest-observed-adverse-effect level; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] This value is the geometric mean of LOAELs from three studies (after application of UFs) and is described in the CalEPA PHG as an estimated safe dose level.

[e] This RfD was developed by route-to-route extrapolation using the PODs from two inhalation neurotoxicity studies {Cavalleri et al., 1994, 195942; Echeverria, 1995, 195893}. The PODs were 2.6 mg/kg/day {Cavalleri et al., 1994, 195942} and 9.7 mg/kg/day {Echeverria, 1995, 195893}; a UF of 1,000 was applied to each of the PODs to generate RfDs of 0.0026 and 0.0097 mg/kg/day, respectively. The RfD in the table represents the midpoint of the two candidate RfDs.

[f] "Likely to be carcinogenic in humans by all routes of exposure," based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

[g] This value was derived based on route-to-route extrapolation from the chronic inhalation study by Cavalleri et al. (1994, 195942).

[h] This assessment defers to the corresponding information from the EPA IRIS Toxicological Review listed above.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as tetrachloroethylene. The OPPT Risk Evaluation for Tetrachloroethylene was finalized in December 2020 {U.S. EPA, 2020m, 6311014}, which is after the SYR 4 cut-off date of November 2020 that was used for the health assessment identification process (see Section 4.1.1). During the next SYR cycle (SYR 5), the final OPPT risk evaluation for tetrachloroethylene will be considered.

The health assessment selected for SYR 4 is the 2012 EPA IRIS Toxicological Review of Tetrachloroethylene {U.S. EPA, 2012b, 2826528} (bolded in Table 6-150) because this is an EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for tetrachloroethylene. Although more recent health assessments for tetrachloroethylene were available, they either did not evaluate cancer (ATSDR (2019b, 5425314) and HC (2015b, 3049488)) or they relied on the same critical study (MassDEP (2014, 10571053)) that served as the basis for the 2012 IRIS Toxicological Review of Tetrachloroethylene.

In the selected health assessment, EPA selected a two-year inhalation study in Crj:BDF1 mice published by the Japanese Industrial Safety Association (JISA, 1993, 630653) to derive a POD for the oral slope factor. In this study, 400 mice were exposed to tetrachloroethylene at concentrations of 0, 10, 50, and 250 ppm via inhalation for 6 hours a day for 104 weeks. Inhalation data were used to determine the oral slope factor because the only oral bioassay available had limitations that precluded the use of the data for extrapolation to lifetime risk in humans. A harmonized physiologically-based pharmacokinetic (PBPK) model was used for route-to-route extrapolation of the inhalation data to an oral slope factor {Chiu and Ginsberg, 2011, 713689}. Using this model, EPA derived a $BMDL_{10}$ of 47 mg/kg/day for total liver oxidative metabolism, resulting in the oral slope factor of 0.0021 $(mg/kg/day)^{-1}$ for hepatocellular adenomas or carcinomas.

Following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA has described tetrachloroethylene as "likely to be carcinogenic in humans by all routes of exposure," which corresponds to a cancer classification of L {U.S. EPA, 2012b, 2826528}. Because tetrachloroethylene is classified as "likely to be carcinogenic to humans," the available noncancer toxicity values were not evaluated for potential MCLG derivation.

6.2.11.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope of the Risk Evaluation for Perchloroethylene (ethene, 1,1,2,2-Tetrachloro-) which was March 2017 {U.S. EPA, 2020l, 7697272}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for tetrachloroethylene was defined as one year prior to March 2017 resulting in a search date range from March 1, 2016 to January 25, 2022.

From this literature search, 1,165 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Twenty-five of these 1,165 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 1,140 of the 1,165 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-151.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for tetrachloroethylene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-151. Evidence Stream Heat Map Results for Tetrachloroethylene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	301
Environmental Fate	–	469
Human	All	451
	Epidemiologic Quantitative Analyses	80
In Vitro	–	522
No Tag	–	37
Total Unique Studies		**1,140**

Notes:
[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.11.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-152 shows the comparison of the basis for the existing and potential MCLGs for tetrachloroethylene.

Table 6-152. Comparison of the Basis for the Existing and Potential MCLGs for Tetrachloroethylene

Reference	Critical Study	Critical Effect	Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1991a, 5499)	–	–	–	–[d]	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2012b, 2826528)	JISA (1993, 630653)	mononuclear cell leukemia	0.0021	L	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] Though no cancer descriptor was assigned at promulgation, EPA determined that tetrachloroethylene was a Category I chemical for the purpose of establishing an MCLG, due to "strong evidence of carcinogenicity through ingestion."

6.2.11.5 SYR 4 Health Effects Conclusion

The existing NPDWR for tetrachloroethylene was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on strong evidence of carcinogenicity, EPA set the MCLG at zero. A formal cancer descriptor was not assigned at that time. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the U.S. EPA IRIS Toxicological Review {U.S. EPA, 2012b, 2826528} because this is the most recently published EPA health assessment that used the best available science in its evaluation of cancer risk and its derivation of a cancer slope factor for tetrachloroethylene. Based on the analysis and conclusion presented in this health assessment, the CSF was determined to be 0.0021 $(mg/kg/day)^{-1}$ and EPA assigned tetrachloroethylene a cancer classification of L, "likely to be carcinogenic to humans" by all routes of exposure, according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005, 10263976}. For tetrachloroethylene, the more recent cancer descriptor of L, "likely to be carcinogenic to humans," would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.2.12 1,1,2-Trichloroethane (CAS# 79-00-5 | DTXSID5021380)

6.2.12.1 Basis of the Existing MCLG

EPA published the current NPDWR for 1,1,2-trichloroethane on July 17, 1992 {U.S. EPA, 1992g, 10587719}. The NPDWR established an MCLG of 0.003 mg/L and an MCL of 0.005 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.004 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992a, 1664368}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA 1986a, 199530}. A risk management safety factor of 10 was applied in the calculation of the MCLG to account for possible carcinogenicity {U.S. EPA, 1992g, 10587719} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor). The NPDWR set an MCL of 0.005 mg/L based on analytical feasibility {U.S. EPA, 1992g, 10587719}.

6.2.12.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for 1,1,2-trichloroethane that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-153.

Table 6-153. Assessments Identified for 1,1,2-Trichloroethane

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA IRIS Chemical Assessment {U.S. EPA, 1987pp, 5113320}[d]	0.004	NOAEL	White et al. (1985, 64564); Sanders et al. (1985, 64556)	0.057	NCI (1978c, 64554)	C[e]
EPA OW Health Advisory {U.S. EPA, 1989i, 10532726}	0.004	NOAEL	White et al. (1985, 64564); Sanders et al. (1985, 64556)	–[f]	–	C[e]
EPA OW Drinking Water Criteria Document {U.S. EPA, 1992a, 664368}	**0.004**	**NOAEL**	**White et al. (1985, 64564); Sanders et al. (1985, 64556)**	**–[g]**	**–**	**C[e]**

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
ATSDR Toxicological Profile; ATSDR Addendum {ATSDR, 2010b, 5160124}[h]	0.04[i]	NOAEL	White et al. (1985, 64564)	Refer to IRIS[j]	–	–
CalEPA PHG {CalEPA, 2006d, 10489848}	–[k]	NOAEL	White et al. (1985, 64564)	Refer to IRIS	–	–
EPA ORD PPRTV {U.S. EPA, 2011f, 1257697}	Refer to IRIS	–	–	Refer to IRIS	–	–

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level.
[a] Selected health assessment and chronic toxicity value bolded; dash (–) = not provided.
[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "Oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), or tolerable daily intake (TDI).
[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[d] Carcinogenicity assessment last revised in 1987 {U.S. EPA, 1987pp, 5113320}; oral RfD last revised in 1988 {U.S. EPA, 1987pp, 5113320}.
[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.
[f] This assessment did not derive a CSF but reports a value of 0.0573 $(mg/kg/day)^{-1}$ derived by EPA (1980, 29430).
[g] This assessment did not derive a CSF but reports an increased lifetime cancer risk of 10^{-5} in a 70-kg adult at 2.06 µg/L.
[h] Toxicological Profile published in 1989 {ATSDR, 1989b, 664390} with addendum update in 2010 {ATSDR, 2010b, 5160124}.
[i] Intermediate-duration oral MRL; a chronic oral MRL was not derived. The assessment does not state why a chronic oral MRL was not derived, but states that the only chronic oral study identified was NCI (1978c, 64554). The 2010 Addendum provides new supporting data but does not change the MRLs derived in the 1989 Toxicological Profile.
[j] This assessment defers to the corresponding IRIS information listed above.
[k] CalEPA uses a UF of 10,000 for 1,1,2-trichloroethane. Reference value could not be derived since the EPA applies a maximum UF of 3,000.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as 1,1,2-trichloroethane. However, the OPPT risk evaluation for 1,1,2-trichloroethane is ongoing (the Final Scope of the Risk Evaluation for 1,1,2-Trichloroethane was finalized in August of 2020) and was therefore not selected. If finalized by the cut-off date for identifying assessments in the next SYR cycle (SYR 5), it will be considered.

The health assessment selected for SYR 4 is the OW Drinking Water Criteria Document for 1,1,2-Trichloroethane {U.S. EPA, 1992a, 664368} (bolded in Table 6-153) because it is an EPA assessment that derives an oral toxicity value and used the best available science in its evaluation of 1,1,2-trichoroethane toxicity. Although more current health assessments were available {ATSDR, 2010b, 5160124; CalEPA, 2006d, 10489848; U.S. EPA, 2011f, 1257697}, those assessments were based on the same critical studies {White et al. 1985, 64564; Sanders et al. 1985, 6455} and/or were based on the toxicity value derived by the selected OW Drinking Water Criteria Document for 1,1,2-Trichloroethane {U.S. EPA, 1992a, 664368}.

The 1992 OW Drinking Water Criteria Document derived an oral RfD using data from two subchronic mouse studies {White, 1985, 64564; Sanders, 1985, 64556}. In these studies, CD-1 mice of both sexes were exposed to 0, 20, 200, or 2000 mg/L (resulting in intakes of 0, 4.4, 46, and 305 mg/kg/day for males and 0, 3.9, 44, and 384 mg/kg/day for females) of 1,1,2-trichloroethane in drinking water for 90 days. A

NOAEL of 20 mg/L (3.9 mg/kg/day for female mice) was determined from serum clinical chemistry data showing decreased humoral immune response (i.e., significantly altered leukocytes, hematocrit, and hemoglobin levels). A total uncertainty factor (UF) of 1000 was applied to this POD: 10 for interspecies variability, 10 for intraspecies variability, and 10 for extrapolation from subchronic to chronic exposure. After applying the total UF, the chronic oral RfD was calculated to be 0.004 mg/kg/day{U.S. EPA, 1992g, 10587719}.

Based on available information and following the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, EPA determined that 1,1,2-trichloroethane is a "possible human carcinogen," which corresponds to a "C" classification {U.S. EPA, 1992a, 664368}.

6.2.12.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT Final Scope Risk Evaluation for 1,1,2-trichloroethane which was September 2019 {U.S. EPA, 2020n, 10565933}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for 1,1,2-trichloroethane was defined as one year prior to September 2019 resulting in a search date range from September 1, 2018 to September 27, 2022.

From this literature search, 13 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Following SWIFT-Review, all 13 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-154.

In the future, the relevant peer reviewed literature identified may be used to further EPA's understanding of health effects for 1,1,2-trichloroethane and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-154. Evidence Stream Heat Map Results for 1,1,2-Trichloroethane[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	1
Environmental Fate	–	9
Human	All	5
	Epidemiologic Quantitative Analyses	1
In Vitro	–	3
No Tag	–	1
Total Unique Studies		**13**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.12.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-155 shows the comparison of the basis for the existing and potential MCLGs for 1,1,2-trichloroethane.

Table 6-155. Comparison of the Basis for the Existing and Potential MCLGs for 1,1,2-Trichloroethane

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992a, 664368)	–	–	–[d]	C	–	–	–	–	–	–
EPA (1992a, 664368)	Sanders et al. (1985, 64550); White et al. (1985, 64564)	Adverse effects on the liver, depressed humoral immune status	–	–	0.004	20%	General Population	70 kg adult, 2 L/day	0.003[e]	–
Relevant Health Assessment Identified in SYR 4										
EPA (1992a, 664368)	–	–	–	C	–	–	–	–	–	–
EPA (1992a, 664368)	Sanders et al. (1985, 64550); White et al. (1985, 64564)	Adverse effects on the liver, depressed humoral immune status	–	–	0.004	20%	General Population	33.8 mL/kg/ day	–	0.002[e,f]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] 57 FR 31776 does not indicate the CSF that was used as part of the decision to assign a safety factor value of 1, 3, or 10 {U.S. EPA, 1992g, 10587719}.
[e] This MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity.
[f] The difference from Original MCLG based only on use of updated drinking water intake values {U.S. EPA, 2019, 7267482}

6.2.12.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 1,1,2-trichloroethane was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.004 mg/kg/day {U.S. EPA, 1992a, 664368} DWI and BW values for the general population (i.e., 2 L/day and 70 kg) and an RSC of 20%, as well as applying an additional risk management safety factor of 10 to account for possible carcinogenicity (see Table 3-1 for more information on cancer classification and application of a risk management safety factor), EPA set the MCLG at 0.003 mg/L and assigned 1,1,2-trichloroethane a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992a, 664368}, according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA followed the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2. Although new health assessments were identified, those assessments were based on the same critical study and/or referenced the toxicity value derived by the selected OW Criteria Document {U.S. EPA, 1992a, 664368}. Therefore, EPA selected the OW Criteria Document {U.S. EPA, 1992a, 664368} used to support the NPDWR at rule promulgation because it is an EPA assessment that derives an oral toxicity value and used the best available science in its evaluation of 1,1,2-trichoroethane toxicity. In this cycle of review, 1,1,2-trichloroethane maintained the cancer classification of C, "possible human carcinogen." Therefore, this potential MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity. Based on an RfD of 0.004 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (all ages) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.002 mg/L. EPA concluded that, there is no health effects information available to impact the MCLG, however there is a potential to lower the existing MCLG from 0.003 mg/L to support a change to the potential MCLG of 0.002 mg/L based on the updated exposure factor of 33.8 mL/kg/day for the general population.

6.2.13 Trichloroethylene (CAS# 79-01-6 | DTXSID0021383)

6.2.13.1 Basis of the Existing MCLG

EPA published the current NPDWR for trichloroethane on July 8, 1987 {U.S. EPA, 1987m, 3809376}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen" based on sufficient animal evidence of carcinogenicity and inadequate human evidence {U.S. EPA, 1987m, 3809376} according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.005 mg/L based on the practical quantitation limit {U.S. EPA, 1987m, 3809376}.

6.2.13.2 Results of the SYR 4 Health Assessment Search

The following table shows the identified final, health assessments relevant to chronic toxicity available for trichloroethylene (TCE) that were published prior to the cut-off date of November 2020 for the qualifying health assessments search. The health assessment selected for SYR 4 is bolded in Table 6-156.

Table 6-156. Assessments Identified for Trichloroethylene

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OW Drinking Water Criteria Document {U.S. EPA, 1985k, 10509760}	0.007[d]	LOAEL	Kimmerle and Eben (1973, 75320)	–	–	–
EPA OW Health Advisory {U.S. EPA, 1987qq, 10510379}	0.00735[e]	LOAEL	Kimmerle and Eben (1973, 75320)	–	–	B2[f]
WHO GDWQ {WHO, 2005b, 10509454}	0.00146	$BMDL_{10}$	Dawson et al. (1993, 701708)	–	–	–
HC GDWQ {HC, 2005, 3827435}	0.00146	$BMDL_{10}$	Dawson et al. (1993, 701708)	–	–	–[g]
CalEPA PHG {CalEPA, 2009c, 3840126}	0.5	BMD_{10}	Haag-Gronlund et al. (1995, 702259)	0.0059[h]	NCI (1976, 75178); Maltoni et al. (1986, 196223)	–
EPA IRIS Toxicological Review {U.S. EPA, 2011d, 3532116}	0.0005[i]	HED_{99},LOAEL	Keil et al. (2009, 486801)	**0.046[j]**	**Charbotel et al. (2006, 729633)**	**H[k]**
		LOAEL	Peden-Adams et al. (2006, 707381);			
		HED_{99},$BMDL_{01}$	Johnson et al. (2003, 700526)			
ATSDR Toxicological Profile {ATSDR, 2019c, 5348341}	Refer to IRIS[l]	Refer to IRIS	Refer to IRIS	Refer to IRIS	Refer to IRIS	Refer to IRIS
EPA OCSPP Risk Evaluation {U.S. EPA, 2020o, 5176430}	-	-	-	0.05[m]	Charbotel et al. (2006, 729633)	H[k]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided; BMD_{10} = benchmark dose level at the 95% lower confidence limit corresponding to a 10% response; HED_{99},LOAEL = the 99th percentile (due to human toxicokinetic uncertainty and variability) human equivalent dose (HED) to the mouse LOAEL using the internal dose metric of trichloroethylene metabolized/$kg^{3/4}$/day; HED_{99},$BMDL_{01}$ = the 99th percentile (due to human toxicokinetic uncertainty and variability) HED to the rat internal dose $BMDL_{01}$ (BMDL associated with a 1% extra risk on a pup basis) of 0.0142 mg trichloroethylene oxidized/$kg^{3/4}$/day; ATSDR = Agency for Toxic Substances and Disease Registry.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value." "Oral reference value" can refer to the acceptable daily intake (ADI), minimal risk level (MRL), point of departure/uncertainty factor (POD/UF), reference dose (RfD), acceptable daily dose (ADD), or tolerable daily intake (TDI).
[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.
[d] The RfD of 0.007 mg/kg/day is based on a 14-week inhalation study in rats and was calculated by EPA Health and Ecological Criteria Division (HECD) using the RfD of 0.514 mg/day reported in EPA (1985k, 10509760) and a default body weight of 70 kg.
[e] This RfD is based on a 14-week inhalation study in rats.
[f] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.
[g] This assessment did not designate a cancer descriptor based on EPA's cancer guidelines, but states that trichloroethylene is classified in Group II (probably carcinogenic to humans).
[h] Based on the geometric mean of CSF values from an oral gavage study {NCI, 1976, 75178} and inhalation study {Maltoni et al., 1986, 196223}, which was identified in the CalEPA assessment as most appropriate for use in calculating a PHG.
[i] The IRIS assessment notes that this RfD was derived as a midpoint of three similar candidate RfDs—0.00048 mg/kg/day for decreased thymus weight in mice {Keil et al., 2009, 486801}, 0.00037 mg/kg/day for developmental immunotoxicity in mice {Peden-Adams et al., 2006, 707381}, and 0.00051 mg/kg/day for fetal heart malformations in rats {Johnson et al., 2003, 700526}.
[j] This oral CSF was derived using a human physiologically based pharmacokinetic model to extrapolate from the inhalation unit risk estimate, which was based on human kidney cancer risks reported in Charbotel et al. (2006, 729633) and adjusted for potential risk for cancers at multiple sites.
[k] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.
[l] This assessment defers to the corresponding IRIS information listed above. This profile also states that 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.
[m] This oral slope factor is based on the oral slope factor of 0.0464 per mg/kg/day derived in EPA (2011d, 3532116), rounded to on significant figure for an oral slope factor of 0.05 per mg/kg/day.

Following the decision-logic provided in the health assessment selection criteria (see Section 4.1.2), OPPT risk evaluations are preferred for regulated industrial chemicals such as trichloroethylene. The 2020 OPPT Risk Evaluation for Trichloroethylene was finalized by the SYR 4 cut-off date of November 2020 and was among the assessments considered for SYR 4 {U.S. EPA, 2020o, 5176430}. However, the CSF derived in the 2020 OPPT Risk Evaluation for Trichloroethylene is based on the CSF derived in the 2011 EPA IRIS Toxicological Review for trichloroethylene and, therefore, does not introduce new science {U.S. EPA, 2011d, 3532116}. Therefore, the health assessment selected for SYR 4 is the 2011 EPA IRIS Toxicological Review for Trichloroethylene {U.S. EPA, 2011d, 3532116}.

The 2011 IRIS health assessment identified a high-quality occupational case-control study of renal cell cancer (RCC) {Charbotel et al., 2006, 729633} as the critical study to derive an inhalation unit risk estimate for TCE, which was subsequently extrapolated to an oral slope factor using a PBPK model. In this epidemiological study of 86 incident RCC cases and 316 age-and sex-matched controls, a detailed exposure assessment {Fevotte et al., 2006, 729415} determined individual cumulative exposure estimates of TCE. Charbotel et al. (2006, 729633) accounted for several potential confounding factors such as exposure to other chemicals and found a significant dose-response relationship for RCC and cumulative TCE exposure.

The lower confidence limit of the concentration corresponding to an extra risk of 1% (LEC_{01} (lowest effective concentration)) was used for determination of the POD based on epidemiological data {Charbotel, 2006, 729633}. The risk ratio for an extra risk of 1% for RCC incidence is 1.9, which is in the range of the odds ratios reported by Charbotel et al. (2006, 729633). Thus, 1% extra risk was selected for determination of the POD: the LEC_{01} of 1.82 ppm was used as the POD. An inhalation unit risk estimate of 5.49×10^{-3} ppm^{-1} was calculated from the LEC_{01} using a linear low-dose extrapolation, providing an upper bound on the risk of RCC incidence only. A PBPK model-based route-to-route extrapolation of the RCC-specific cancer inhalation unit risk estimate, which adjusted for potential risk for non-Hodgkins lymphoma (NHL) and liver cancer, was then conducted. The summation of the oral

slope factor estimates for RCC, NHL, and liver cancer resulted in the total oral slope factor of 0.0464 $(mg/kg/day)^{-1}$.

Following the 2005 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}, EPA has described TCE as "carcinogenic in humans," which corresponds to a cancer classification of H {U.S. EPA, 2011d, 3532116}. Because TCE is classified as "carcinogenic to humans," the available noncancer toxicity values were not considered for potential MCLG derivation.

6.2.13.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. Under the TSCA, EPA's OPPT conducts risk evaluations to determine whether a chemical presents unreasonable risk of injury to the environment or human health {U.S. EPA, 2017f, 6128248}. For SYR 4, EPA relied on the literature search cut-off date indicated in the OPPT risk evaluation for trichloroethylene which was March 2017 {U.S. EPA, 2020o, 5176430}. The start date of the SYR 4 literature search conducted in PubMed and Web of Science for trichloroethylene was defined as one year prior to March 2017 resulting in a search date range from March 3, 2016 to September 30, 2022.

From this literature search, 805 potentially relevant unique studies were identified following deduplication. SWIFT-Review software {Howard, 2016, 4149688}, which utilizes statistical text mining and machine learning methods, was used to categorize studies by evidence streams relevant to human health. Studies from the following evidence streams in SWIFT-Review were included: Human (Epidemiological Quantitative Analyses), Animal (Human Health Models), Environmental Fate, and In Vitro. Nineteen of these 805 unique studies were categorized to an evidence stream not used for this project (e.g., Animal (All), Ecotoxicity (Animal and Plant), Plant, Physical Chemistry) and therefore, were excluded from further consideration (see Section 4.3.1.3 for further information). Following SWIFT-Review, 786 of the 805 unique studies were categorized to the human health-relevant evidence streams shown in Table 6-157.

In the future, the relevant peer-reviewed literature identified may be used to further EPA's understanding of health effects for trichloroethylene and specifically to inform EPA prioritization processes (see Exhibit 3.2 in EPA's Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}).

Table 6-157. Evidence Stream Heat Map Results for Trichloroethylene[a]

Tag	Sub Tag	Number of Studies
Animal	Human Health Models	175
Environmental Fate	–	448
Human	All	348
	Epidemiologic Quantitative Analyses	84
In Vitro	–	243
No Tag	–	24
Total Unique Studies		**786**

Notes:

[a] Evidence streams in SWIFT-Review relevant to animals and/or humans were used for tagging. SWIFT-Review analyzed the titles and abstracts using machine learning and statistical text mining methods to tag studies to Animal (Human Health Models), Environmental Fate, Human (All), Human (Epidemiological Quantitative Analyses), In Vitro, and No Tag.

Refer to Section 4.3 for detailed information on literature search and screening methods including date limit selection. For literature search strings, search parameters, and SWIFT-Review details, see Appendix C.

6.2.13.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-158 shows the comparison of the basis for the existing and potential MCLGs for trichloroethylene.

Table 6-158. Comparison of the Basis for the Existing and Potential MCLGs for Trichloroethylene

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation								
EPA (1987qq, 10510379)	NCI (1976, 75178); NTP (1982d, 10754288)	Liver neoplasms in mice	–	B2	–	–	0	–
Relevant Health Assessment Identified in SYR 4								
EPA (2011d, 3532116)	Charbotel et al. (2006, 729633)	Renal cell carcinoma, non-Hodgkin's lymphoma, and liver tumors	0.046	H	–	–	–	0

Notes: NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.2.13.5 SYR 4 Health Effects Conclusion

The existing NPDWR for trichloroethylene was published on July 8, 1987 {U.S. EPA, 1987m, 3809376}. Based on a cancer classification of B2, "probable human carcinogen," EPA set the MCLG to zero {U.S. EPA, 1987m, 3809376}. Following the health assessment search and selection protocols outlined in Sections 4.1.1 and 4.1.2, EPA selected the EPA IRIS Toxicological Review {U.S. EPA, 2011d, 3532116} to derive the potential MCLG because the 2020 OPPT Risk Evaluation for Trichloroethylene is based on the same cancer study as the 2011 EPA IRIS Toxicological Review for trichloroethylene and the CSFs are numerically the same (although the OPPT assessment is rounded to one significant digit) {U.S. EPA, 2011d, 3532116}. Based on the analysis and conclusion presented in the 2011 IRIS Toxicological Review, the CSF was set at 0.046 $(mg/kg/day)^{-1}$ and the cancer classification was updated to H, "carcinogenic to humans," by all routes of exposure, following EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. For trichloroethylene, the more recent cancer descriptor of H, "carcinogenic to humans," would also lead to an MCLG of zero; therefore, more recent information does not support a change to the MCLG.

6.3 Active Pesticides

6.3.1 Alachlor (CAS# 15972-60-8 | DTXSID1022265)

6.3.1.1 Basis of the Existing MCLG

EPA published the current NPDWR for alachlor on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established an MCLG of zero based on a cancer classification of B2, "probable human carcinogen," for inadequate evidence of carcinogenicity from human studies and sufficient evidence from animal studies {U.S. EPA, 1985d, 3809374} according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification). The NPDWR also established an MCL of 0.002 mg/L based on analytical feasibility {U.S. EPA, 1991a, 5499}.

6.3.1.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for atrazine that was published prior to the cut-off date of November, 2020 from EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-161).

Table 6-159. Most Recent OPP HHRA Identified for Alachlor

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Value[c]	Oral Critical Cancer Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2007b, 10492629}	0.01	NOAEL	Monsanto Co. (1984, 11272605)	**0.005**	**Stout et al. (1984, 10709980)[d]**	**L/N[e]**

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference value expressed in mg/kg/day and refers to the chronic population-adjusted dose (cPAD).

[c] Cancer value expressed in mg/kg/day and refers to point of departure/uncertainty factor (POD/UF) based on a Margin-of-Exposure (MOE) approach {U.S. EPA, 2007a, 10492629}.

[d] The study appears to be Stout et al. (1984, 10709980) based on the same critical endpoints and study design outlined in the 1987 EPA Office of Drinking Water Health Advisory for Alachlor {U.S. EPA, 1987l, 10509768}.

[e] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA determined that alachlor is "not likely to be carcinogenic to humans at low doses but likely to be carcinogenic at high doses" by all routes of exposure {U.S. EPA, 2007a, 10492629}.

The health assessment selected for SYR 4 is the 2007 EPA OPP HHRA {U.S. EPA, 2007b, 10492629} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as alachlor (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The EPA OPP HHRA for alachlor identified a chronic dietary study in Long-Evans rats {Stout, 1984, 10709980} as the critical study and source of the POD. Groups of 50 male and 50 female rats were fed 0, 0.5, 2.5, or 15 mg/kg/day technical alachlor for two years. A statistically significant increase in the incidence of nasal respiratory epithelium adenomas was observed in both sexes dosed with 15 mg/kg/day. In addition, one female in the 2.5 mg/kg/day group had a nasal respiratory epithelium adenoma; this finding was considered toxicologically relevant due to the rarity of these neoplasms and the significantly increasing incidence trend, and was the basis for a NOAEL of 0.5 mg/kg/day {U.S. EPA, 2007b, 10492629}. EPA determined that the mode of action of alachlor for the development of these nasal tumors is non-linear and non-mutagenic {U.S. EPA, 2007a, 10492629}. Therefore, EPA calculated an RfV from the 0.5 mg/kg/day POD using a margin-of-exposure (MOE) approach in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. Because of the threshold approach that is being used for risk assessment, a total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the oral RfV was calculated to be 0.005 mg/kg/day for alachlor.

EPA determined that alachlor is "not likely to be carcinogenic to humans at low doses but likely to be carcinogenic at high doses" by all routes of exposure, based on evidence demonstrating nonlinear mechanisms of carcinogenicity in rats that require precursor toxicity events for formation. An MOE approach was therefore recommended by the HED Cancer Assessment Review Committee (CARC) for assessment of human cancer risk {U.S. EPA, 2007b, 10492629}.

6.3.1.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.1.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-160 shows the comparison of the basis for the existing and potential MCLGs for alachlor.

Table 6-160. Comparison of the Basis for Existing and Potential MCLGs for Alachlor

Reference	Critical Study	Critical Effect	Oral RfV[a]	Cancer Descriptor	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation									
EPA (1985d, 3809374)	Stout et al. (1984, 10709980)	Increased incidence of nasal adenomas in rats	–	B2[d]	–	–	–	0	–
Relevant Health Assessment Identified in SYR 4									
EPA (2007b, 10492629)	–	–	–	L/N	–	–	–	–	–
EPA (2007b, 10492629)	Stout et al. (1984, 10709980)	Increased incidence of nasal adenomas in rats	0.005[e]	–	20%	General Population	33.8 mL/kg/day	–	0.03

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] The IARC classified alachlor in Group 3, inadequate evidence for carcinogenicity in humans and inadequate evidence for carcinogenicity in animals, before the results of feeding studies in mice and rats were available. Alachlor was later classified in EPA's Group B2, according to EPA's Proposed Guidelines for Risk Assessment, based upon the incidence of tumors of the nasal epithelium, stomach and thyroid from the feeding study in rats {Stout et al., 1984, 10709980}. EPA proposed a MCLG of zero based on an estimated lifetime cancer risk rate of 0.15 µg/L derived from EPA OPP {U.S. EPA, 1985d, 3809374}.

[e] The selected endpoint for risk assessment has been attributed to a non-linear, non-mutagenic mode of action. Thus, as per the 2005 EPA Cancer Guidelines {U.S. EPA, 2005d, 10263976}, a Margin-of-Exposure (MOE) calculation was used as one would do for a threshold noncancer toxicity risk assessment. As this MOE threshold value is more sensitive than the cPAD, this value was selected for SYR 4.

6.3.1.5 SYR 4 Health Effects Conclusion

The existing NPDWR for alachlor was promulgated on January 30, 1991 {U.S. EPA, 1991a, 5499}. EPA set the MCLG at zero based on a cancer classification of B2, "probable human carcinogen" {U.S. EPA, 1985d, 3809374}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the EPA OPP HHRA {U.S. EPA, 2007b, 10492629} to derive the potential MCLG because it is the most recent EPA OPP HHRA. Because a linear dose-response extrapolation, which was the basis of the existing MCLG of zero, is no longer considered appropriate in this case, an MOE approach was recommended by the HED Cancer Assessment Review Committee (CARC) for assessment of human cancer risk. Based on a POD/UF of 0.005 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection) and an RSC of 20 percent, EPA calculated a potential MCLG of 0.03 mg/L. Based on the analysis and conclusion presented in the OPP HHRA, EPA updated the cancer classification for alachlor to L/N, "not likely to be carcinogenic to humans at low doses but likely to be carcinogenic at high doses," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005, 10263976}. For alachlor, more recent information does not support a change to the MCLG.

6.3.2 Atrazine (CAS# 1912-24-9 | DTXSID9020112)

6.3.2.1 Basis of the Existing MCLG

EPA published the current NPDWR for atrazine on January 30, 1991 {U.S. EPA, 1991a, 5499}. The NPDWR established both an MCLG and an MCL of 0.003 mg/L based on a reference dose of 0.005 and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1990i, 11311206}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. The MCLG was derived using the RfD approach and applying an additional risk management safety factor of 10 to account for possible carcinogenicity {U.S. EPA, 1991a, 5499} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.3.2.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for atrazine that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-161).

Table 6-161. Most Recent OPP HHRA Identified for Atrazine

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2018a, 10533087}[d]	**0.076[e]**	**$BMDL_{1SD}$**	**Cooper et al. (2010, 10534153)[f]**	–	–	N[g]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; $BMDL_{1SD}$ = benchmark dose level corresponding to a change in the mean response equal to one standard deviation from the control; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference value expressed in mg/kg/day and refers to the acute population-adjusted dose (aPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.[d] While this OPP assessment document is labeled "draft," it is considered final at the time of publication in the Federal Register (Richard Fehir, pers. comm). OPP assessments can be updated at any time based on the availability of new scientific information.

[e] A 4-day aPAD for females aged 13 to 49 years was used as the RfV, as this was the exposure duration that elicited a response in the critical study, and longer exposure durations did not lead to greater toxicity.

[f] This study assessed oral, dermal, and inhalation exposures. Atrazine, propazine, and simazine have common metabolites, and EPA determined that they share a common neuroendocrine mechanism of toxicity and constitute the triazine common mechanism group.
[g] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2018 EPA OPP HHRA {U.S. EPA, 2018a, 10533087} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as atrazine (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The 2018 EPA OPP HHRA identified a subacute study {Cooper, 2010, 10534153} as the critical study and source of the POD. The study examined the effects of atrazine exposure on regularly cycling female rats over a four-day period (day of vaginal estrus through the day after proestrus) at doses of 0, 1.56, 3.12, 6.25, 12.5, 25, or 75 mg/kg/day. A statistically significant attenuation of the pre-ovulatory luteinizing hormone (LH) surge was observed at ≥ 3.12 mg/kg/day. EPA used BMD modeling to derive a $BMDL_{1SD}$ (BMD lower bound of the confidence limit) of 2.42 mg/kg/day based on attenuation of the LH surge {U.S. EPA, 2018a, 10533087}.

A physiologically-based pharmacokinetic (PBPK) model was used to extrapolate the $BMDL_{1SD}$ for atrazine based on the animal study to a toxicologically-relevant internal metric (i.e., the average TCT (total chlorotriazines) concentration in plasma) for different human subpopulations. The PBPK model was parameterized to include growth from birth to adulthood for dietary exposures. PODs for three different human subpopulations, children (ages 6–12), youth (ages 13–19), and females (ages 13–49), were derived for exposures of four days or longer because decreased LH surge in rats was observed after four days in the study {Cooper et al., 2010, 10534153}. Further, research suggests that longer exposures to atrazine are not expected to result in greater toxicity {U.S. EPA, 2018a, 10533087}. EPA subsequently used the lowest POD, 2.29 mg/kg/day, for the most sensitive subpopulation, females (ages 13–49), as the basis to derive the RfV. A total uncertainty factor (UF) of 30 was applied to the POD: 3 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the four-day population adjusted dose (PAD) for females (ages 13–49) was calculated to be 0.076 mg/kg/day {U.S. EPA, 2018a, 10533087}.

EPA reported that atrazine is "not likely to be carcinogenic to humans" according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976} based on the overall weight of evidence including epidemiological data and mode of action considerations {U.S. EPA, 2018a, 10533087}.

6.3.2.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.2.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-162 shows the comparison of the basis for the existing and potential MCLGs for atrazine.

Table 6-162. Comparison of the Basis for the Existing and Potential MCLGs for Atrazine

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1990i, 11311206)	–	–	–	C	–	–	–	–	–	–
EPA (1990i, 11311206)	Ciba-Geigy (1987, 1303888)	Decreased body weights of rat pups in the second generation at the time of weaning	–	–	0.005	20%	General Population	70 kg adult, 2 L/day	0.003	–
Relevant Health Assessment Identified in SYR 4										
EPA (2018a, 10533087)	–	–	–	N	–	–	–	–	–	–
EPA (2018a, 10533087)	Cooper (2010, 10534153)	Attenuation of the luteinizing hormone surge	–	–	0.076[d]	20%	Females aged 13–49 years[e]	35.6 mL/kg/day[f]	–	0.4[g]

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] A four-day PAD for females aged 13–49 years was used as the RfV as this is the duration it takes to elicit a response in rats, and longer durations do not lead to greater toxicity.

[e] Target population is females aged 13–49 years as indicated in EPA (2018d, 10533021).

[f] Drinking water intakes for females aged 13-49 years were calculated using https://fcid.foodrisk.org/percentiles# {JIFSAN, 2023, 10667059}.

[g] EPA updated the cancer classification to N, "not likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. Therefore, the SYR 4 potential MCLG is derived using the RfD approach without an additional risk management safety factor.

6.3.2.5 SYR 4 Health Effects Conclusion

The existing NPDWR for atrazine was published on January 30, 1991 {U.S. EPA, 1991a, 5499} and established an MCLG of 0.003 mg/L. The MCLG was derived based on an RfD of 0.005 mg/kg/day, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), an RSC of 20%, and application of an additional risk management safety factor of 10 to account for possible carcinogenicity of atrazine (based on its assigned cancer classification of C, "possible human carcinogen" {U.S. EPA, 1990i, 11311206}) (see Table 3-1 for more information on cancer classification and application of a risk management safety factor). Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2018a, 10533087} to derive the potential MCLG. Based on a PAD of 0.076 mg/kg/day {U.S. EPA, 2018a, 10533087}, an adjusted DWI-BW ratio of 35.6 mL/kg/day for females of childbearing age (13–49 years) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.4 mg/L. Based on the analysis and conclusion presented in the EPA OPP HHRA, EPA updated the cancer classification to N, "not likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. As a result of this conclusion, the risk management safety factor of 10 was removed when calculating the potential MCLG. EPA concluded that new health effects information supports raising the current MCLG of 0.003 mg/L to the potential MCLG of 0.4 mg/L.

6.3.3 Carbofuran (CAS# 1563-66-2 | DTXSID9020249)

6.3.3.1 Basis of the Existing MCLG

EPA published the current NPDWR for carbofuran on January 30, 1991, establishing both an MCLG and an MCL of 0.04 mg/L {U.S. EPA, 1991a, 5499}. EPA based the MCLG on a reference dose of 0.005 mg/kg/day and a cancer classification of E, "evidence of non-carcinogenicity for humans" {U.S. EPA, 1987rr, 10228499} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.3.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for carbofuran that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (see Table 6-163).

Table 6-163. Most Recent OPP HHRA Identified for Carbofuran

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2008a, 10494332}	**0.00006[d]**	**$BMDL_{10}$**	**FMC Corporation (2005, 10710055); FMC Corporation (2007, 10710054); EPA (2007c, 10492651)**	–	–	N[e]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference value expressed in mg/kg/day and refers to the acute population-adjusted dose (aPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] No chronic oral RfD value was derived. The EPA OPP HHRA states that the aPAD is considered protective of chronic exposures because carbofuran-induced inhibition of AChE activity is reversible (within 24 hours) and longer-term exposures can be considered as a series of acute exposures.
[e] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2008 EPA OPP HHRA {U.S. EPA, 2008a, 10494332} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as carbofuran (see Section 4.1.2.1 for the decision-logic that was applied for all SYR 4 chemicals).

The 2008 EPA OPP HHRA reports that data from several acute AChE inhibition studies were reviewed for the dietary risk assessment of carbofuran and concluded that data for AChE inhibition in brains of postnatal day 11 (PND 11) rat pups represent the highest quality dataset available. AChE inhibition data for both brain and red blood cells from three studies were combined to conduct a BMD analysis {FMC Corporation, 2005, 10710055; FMC Corporation, 2007, 10710054; U.S. EPA, 2007c, 10492651}. The three studies provide very similar results for brain AChE inhibition but the relative sensitivity of brain and red blood cell (RBC) AChE inhibition remains unknown, although RBC AChE inhibition was more sensitive than brain AChE in one of the three studies {U.S. EPA, 2007c, 10492651}. EPA determined that the RBC AChE data from another of the studies {FMC Corporation, 2007, 10710054} are not reliable for purposes of POD or UF determination {U.S. EPA, 2008a, 10494332}. Therefore, EPA used the $BMDL_{10}$ of 0.03 mg/kg/day based on the PND 11 brain AChE data from combining the three studies as the basis for deriving the POD for infants and children. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 5 for database uncertainties based on the 5-fold difference between brain AChE inhibition in pups and RBC AChE inhibition in adults, which was the more sensitive endpoint in adult rats, the acute population-adjusted dose (aPAD) for carbofuran was calculated to be 0.00006 mg/kg/day. Carbofuran-induced inhibition of AChE has been shown to be reversible (within 24 hours after inhibition). Thus, longer-term exposures could be considered as a series of acute exposures. Therefore, the aPAD is considered protective of chronic exposures {U.S. EPA, 2008a, 10494332}.

EPA reported that carbofuran is categorized as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice or rats {U.S. EPA, 2008a, 10494332} according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

6.3.3.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. OW did not conduct a literature search for pesticides included in SYR 4 that have existing uses and tolerances registered and regulated under FIFRA. As of 2009, EPA canceled uses and revoked carbofuran tolerances due to considerable risks associated with this pesticide in food and drinking water. However, active import tolerances for certain foods (e.g., bananas, coffee, rice, and sugarcane) still exist {U.S. EPA, 2015b, 10666804}. Therefore, OW did not conduct a literature search for carbofuran.

6.3.3.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-164 shows the comparison of the basis for the existing and potential MCLGs for carbofuran.

Table 6-164. Comparison of the Basis for the Existing and Potential MCLGs for Carbofuran

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA, (1987rr, 10228499)	–	–	–	E	–	–	–	–	–	–
EPA, (1987rr, 10228499)	FMC Corporation (1983, 11264443)	RBC and plasma cholinesterase inhibition and testicular and uterine effects in beagle dogs	–	–	0.005	20%	General Population	70 kg adult, 2 L, day	0.04	–
Relevant Health Assessment Identified in SYR 4										
EPA (2008a, 10494332)	–	–	–	N	–	–	–	–	–	
EPA (2008a, 10494332)	FMC Corporation (2005, 10710055); FMC Corporation (2007, 10710054); EPA (2007c, 10492651)	Brain AChE inhibition in PND 11 rat pups	–	–	0.00006[d]	20%	Children aged 0–13 years[e]	43.3 mL/kg/day[f]	–	0.0003

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided; RBC = red blood cell; AChE = acetylcholinesterase; PND = postnatal day.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] No chronic oral RfD value was derived. The EPA OPP HHRA states that the aPAD is considered protective of chronic exposures because carbofuran-induced inhibition of AChE activity is reversible (within 24 hours) and longer-term exposures can be considered as a series of acute exposures.

[e] Target population is children aged 0–13 years as indicated in EPA (2008, 10494332).

[f] Drinking water intakes for children aged 0–13 years were calculated using https://fcid.foodrisk.org/percentiles# {JIFSAN, 2023, 10667059}.

6.3.3.5 SYR 4 Health Effects Conclusion

The existing NPDWR for carbofuran was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.005 mg/kg/day{U.S. EPA, 1987rr, 10228499}, DWI and BW values for the general population (i.e., 70 kg and 2 L/day), and an RSC of 20%, EPA set the MCLG at 0.04 mg/L and designated a cancer classification of E, "evidence of non-carcinogenicity for humans" {U.S. EPA, 1991a, 5499} based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2008a, 10494332} to derive the potential MCLG. Based on an RfD of 0.00006 mg/kg/day {U.S. EPA, 2008a, 10494332}, an adjusted DWI-BW ratio of 43.3 mL/kg/day for children (aged 0–13 years) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.0003 mg/L. Based on the analysis and conclusion presented in the EPA OPP HHRA, the cancer classification was updated to N, "not likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.04 mg/L to the potential MCLG of 0.0003 mg/L.

6.3.4 Diquat (CAS# 85-00-7 | DTXSID3024075)

6.3.4.1 Basis of the Existing MCLG

EPA published the current NPDWR for diquat on July 17, 1992, establishing both an MCLG and an MCL of 0.02 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.0022 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992o, 11311293}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.4.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for diquat that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-165).

Table 6-165. Most Recent OPP HHRA Identified for Diquat

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2020a, 10533339}	**0.005**	**NOAEL**	**ICI Central Toxicology Laboratory (1990, 10535058)[d]**	–	–	E[e]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day and refers to the chronic population-adjusted dose (cPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] The EPA OPP HHRA does not name or provide many details about the critical study (i.e., ICI Central Toxicology Laboratory (1990, 10535058)) from which the RfD is derived, but instead refers to a 2015 EPA OPP HHRA for diquat {U.S. EPA, 2015a, 10533339} for information about the critical study.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 198a6, 199530}.

The health assessment selected for SYR 4 is the 2020 EPA OPP HHRA {U.S. EPA, 2020a, 10533339} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as diquat (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The EPA OPP HHRA identified a chronic toxicity study in dogs {ICI Central Toxicology Laboratory, 1990, 10535058} as the critical study and source of the POD. Beagle dogs were dosed with 0, 0.5, 2.5, or 12.5 mg/kg/day for 52 weeks. Unilateral cataracts were observed in females dosed with 2.5 mg/kg/day, and in both sexes in the 12.5 mg/kg/day groups. EPA derived the RfD using the NOAEL of 0.5 mg/kg/day based on the critical effect of cataracts. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the chronic population-adjusted dose (cPAD) was calculated to be 0.005 mg/kg/day for diquat {U.S. EPA, 2020a, 10533339}.

EPA {U.S. EPA, 2020a, 10533339} categorized diquat as having "evidence for non-carcinogenicity for humans" (Category E) according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on no evidence of carcinogenicity in rats and mice {U.S. EPA, 2020a, 10533339}.

6.3.4.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.4.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-166 shows the comparison of the basis for the existing and potential MCLGs for diquat.

Table 6-166. Comparison of Existing and Potential MCLGs for Diquat

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992o, 11311293)	–	–	–	D	–	–	–	–	–	–
EPA (1992o, 11311293)	Colley (1985, 10754286)	Minimal lens opacity, cataracts in rats	–	–	0.0022	20%	General Population	70 kg adult, 2 L/day	0.02	–
Relevant Health Assessment Identified in SYR 4										
EPA (2020a, 10533339)	–	–	–	E	–	–	–	–	–	–
EPA (2020a, 10533339)	ICI Central Toxicology Laboratory (1990, 10535058)	Cataracts (female dogs)	–	–	0.005	20%	General Population	33.8 mL/kg/day	–	0.03

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.3.4.5 SYR 4 Health Effects Conclusion

The existing NPDWR for diquat was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.0022 mg/kg/day {U.S. EPA, 1992o, 11311293}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.02 mg/L and designated a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992o, 11311293}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2020a, 10533339} to derive the potential MCLG. Based on a PAD of 0.005 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.03 mg/L. Since the time when the existing MCLG was established, EPA has updated the cancer classification for diquat to E, "evidence for non-carcinogenicity for humans," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA concluded that new health effects information supports raising the current MCLG of 0.02 mg/L to the potential MCLG of 0.03 mg/L.

6.3.5 2,4-Dichlorophenoxyacetic acid (2,4-D) (CAS# 94-75-7 | DTXSID0020442)

6.3.5.1 Basis of the Existing MCLG

EPA published the current NPDWR for 2,4-D on January 30, 1991 {U.S. EPA, 1991a, 5499}, establishing both an MCLG and an MCL of 0.07 mg/L. EPA based the MCLG on a reference dose of 0.01 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA 1988k, 11311370}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

6.3.5.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for 2,4-dichlorophenoxyacetic acid (2,4-D) that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-167).

Table 6-167. Most Recent OPP HHRA Identified for 2,4-Dichlorophenoxyacetic acid (2,4-D)

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2017b, 10532862}	**0.21**	**NOAEL**	**Marty et al. (2010, 10524454)**	–	–	D[d]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; OPP = Office of Pesticide Programs; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day unless otherwise specified; "oral reference value" refers to the chronic reference dose (cRfD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

The health assessment selected for SYR 4 is the 2017 EPA OPP HHRA {U.S. EPA, 2017b, 10532862} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as 2,4-D (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides).

The EPA OPP HHRA {U.S. EPA, 2017b, 10532862} identified an oral extended one-generation reproductive toxicity study in rats by Dow Chemical Company {Marty et al., 2010, 10524454} (later published as Marty et al. (2013, 2761941)), as the critical study and source of the POD. In this study, 27 CD Sprague-Dawley (Crl:CD(SD)) rats/sex/dose were exposed to 2,4-D in the diet at concentrations of 0, 100, 300, or 600 (female high dose)/800 (male high dose) ppm (different high-dose levels were selected for males and females based on differences in renal clearance by sex). Dosing through diet started approximately four weeks prior to mating and continued through lactation for F_0 females and up to seven weeks after mating for F_0 males. After weaning, the offspring were exposed to 2,4-D via diet through either postnatal day (PND) 60 (for evaluation of clinical pathology and neurotoxicity, 10/sex/dose), approximately PND 70 (for evaluation of clinical pathology and neurotoxicity, 10/sex/dose; and immunotoxicity, 10/sex/dose), PND 93 (for evaluation of immunotoxicity, 10/sex/dose), or PND 139 (for evaluation of reproductive toxicity, 20/sex/dose). A NOAEL of 300 ppm was identified based on no effects on kidney toxicity. The LOAEL of 600/800 ppm for kidney toxicity (i.e., increased kidney weight and increased incidence of proximal convoluted tubule degeneration) and decreased body weight during lactation was observed in male and female F_1 offspring. EPA converted the 300 ppm diet to a dose of 20.9 or 23.2 mg/kg/day in male and female offspring, respectively. The lower dose in the male offspring was chosen as the NOAEL (i.e., 21 mg/kg/day) to be health protective. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the chronic population-adjusted dose (cPAD) for 2,4-D was calculated to be 0.21 mg/kg/day.

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}, 2,4-D is categorized as Category D, "not classifiable as to human carcinogenicity" based on inadequate evidence from epidemiological and animal studies {U.S. EPA, 1988k, 11311370}.

6.3.5.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.5.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-168 shows the comparison of the basis for the existing and potential MCLGs for 2,4-D.

Table 6-168. Comparison of Existing and Potential MCLGs for 2,4-dichlorophenoxyacetic acid (2,4-D)

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1988k, 11311370)	–	–	–	D	–	–	–	–	–	–
EPA (1988k, 11311370)	Serota et al. (1983, 11273543)	Hematologic, hepatic, and renal toxicity in rats	–	–	0.01	20%	General Population	70 kg adult, 2 L/day	0.07	–
Relevant Health Assessment Identified in SYR 4										
EPA (2017b, 10532862)	–	–	–	D	–	–	–	–	–	–
EPA (2017b, 10532862)	Marty et al. (2010, 10524454)	Renal toxicity in rats	–	–	0.21	20%	General Population	33.8 mL/kg/ day	–	1

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.3.5.5 SYR 4 Health Effects Conclusion

The existing NPDWR for 2,4-D was published on January 30, 1991 {U.S. EPA, 1991a, 5499}. Based on an RfD of 0.01 mg/kg/day {U.S. EPA, 1988k, 11311370}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.07 mg/L and designated a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1988k, 11311370}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2017b, 10532862} to derive the potential MCLG. Based on a PAD of 0.21 mg/kg/day {U.S. EPA, 2017b, 10532862}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20% {U.S. EPA, 2019, 7267482}, EPA calculated a potential MCLG of 1 mg/L. The 2017 EPA OPP HHRA reported a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 2017b, 10532862}, according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA concluded that new health effects information supports raising the current MCLG of 0.07 mg/L.

6.3.6 Endothall (CAS# 145-73-3 | DTXSID7024081)

6.3.6.1 Basis of the Existing MCLG

EPA published the current NPDWR for endothall on July 17, 1992, establishing both an MCLG and an MCL of 0.1 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.02 mg/kg/day {U.S. EPA, 1992p, 11311207} derived from a 24-month feeding study in beagle dogs {Keller, 1965, 11264446} and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992p, 11311207}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.6.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for endothall that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-169).

Table 6-169. Most Recent OPP HHRA Identified for Endothall

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2015a, 10494329}	**0.007**	**LOAEL**	**Trutter (1993, 5935305); Trutter (1995a, 10667446)**	–	–	N[d]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; LOAEL = lowest-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day and refers to the population-adjusted dose (PAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Based on EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}.

The health assessment selected for SYR 4 is the 2015 EPA OPP HHRA {U.S. EPA, 2015a, 10494329} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as endothall (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides).

The 2015 EPA OPP HHRA for endothall identified an unpublished two-generation reproduction study in rats (and its 1995 addendum) {Trutter, 1993, 5935305; Trutter, 1995a, 10667446} as the critical study and source of the POD. Trutter et al. (1993, 5935305) administered 0, 30, 150, or 900 ppm endothall (disodium salt) in the diet to Sprague-Dawley rats (26 rats/sex/dose) for two generations. The critical effect observed in both sexes of F_1 rats at all dose levels was proliferative lesions of the gastric epithelium. A LOAEL of 30 ppm (reported to be equivalent to a dose level of 2 mg/kg/day) was identified based on this finding, and selected as the POD {U.S. EPA, 2015a, 10494329}. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 3 for use of a LOAEL as opposed to a NOAEL, the oral chronic population-adjusted dose (cPAD) was calculated to be 0.007 mg/kg/day for endothall {U.S. EPA, 2015a, 10494329}.

The 2015 EPA OPP HHRA indicated that EPA classified endothall as "not likely to be carcinogenic to humans" according to EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631} based on the lack of evidence of carcinogenicity in mice or rats {U.S. EPA, 2015a, 10494329}.

6.3.6.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.6.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-170 shows the comparison of the basis for the existing and potential MCLGs for endothall.

Table 6-170. Comparison of the Basis for Existing and Potential MCLGs for Endothall

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992p, 11311207)	–	–	–	D	–	–	–	–	–	–
EPA (1992p, 11311207)	Keller (1965, 11264446)	Increased organ weights and organ-to-body weight ratios of the stomach and small intestine in dogs	–	–	0.02	20%	General Population	70 kg adult, 2 L/day	0.1	–
Relevant Health Assessment Identified in SYR 4										
EPA (2015a, 10494329)	–	–	–	N	–	–	–	–	–	–
EPA (2015a, 10494329)	Trutter (1993, 5935305); Trutter (1995b, 10663555)	Proliferative lesions of the gastric epithelium in rats	–	–	0.007	20%	General Population	33.8 mL/kg/ day	–	0.04

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.3.6.5 SYR 4 Health Effects Conclusion

The existing NPDWR for endothall was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.02 mg/kg/day {U.S. EPA, 1992p, 11311207}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.1 mg/L and designated a cancer classification of D {U.S. EPA, 1992p, 11311207}, "not classifiable as to human carcinogenicity," according to the 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2015a, 10494329} to derive the potential MCLG. Based on a PAD of 0.007 mg/kg/day {U.S. EPA, 2015a, 10494329}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.04 mg/L. The OPP HHRA {U.S. EPA, 2015a, 10494329} reported that the cancer classification for endothall was updated to N, "not likely to be carcinogenic to humans," in accordance with EPA's 1999 draft revised guidelines for carcinogen risk assessment {U.S. EPA, 1999c, 41631}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.1 mg/L to the potential MCLG of 0.04 mg/L.

6.3.7 Glyphosate (CAS# 1071-83-6 | DTXSID1024122)

6.3.7.1 Basis of the Existing MCLG

EPA published the current NPDWR for glyphosate on July 17, 1992, establishing both an MCLG and an MCL of 0.7 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.1 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1989j, 10328171}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.7.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for glyphosate that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-171).

Table 6-171. Most Recent OPP HHRA Identified for Glyphosate

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2017c, 10532909}[d]	**1.0**	**NOAEL**	**Moxon (1996, 10489874)**	–	–	N[e]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observable-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference value expressed in mg/kg/day and refers to the chronic population-adjusted dose (cPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] While this OPP assessment document is labeled "draft," it is considered final at the time of publication in the Federal Register (Richard Fehir, pers. comm). OPP assessments can be updated at any time based on the availability of new scientific information.

[e] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2017 EPA OPP HHRA {U.S. EPA, 2017c, 10532909} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances,

such as glyphosate (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides).

The EPA OPP HHRA for glyphosate identified a chronic developmental dietary study in rabbits {Moxon, 1996, 10489874} as the critical study and source of the POD. Female rabbits were dosed with 0, 100, 175, or 300 mg/kg/day via oral gavage during gestational days 7–19. Diarrhea and few and/or no feces were observed in pregnant does treated with ≥ 175 mg/kg/day. Diarrhea was also observed in another developmental study in rabbits at doses of 175 and 350 mg/kg/day {Rodwell, 1980, 10568382}. EPA considered this diarrhea finding to be the critical effect as it was observed at the lowest dose and in a dose-dependent manner in two developmental rabbit studies. The NOAEL of 100 mg/kg/day based on the incidence of maternal diarrhea was used as the POD {Moxon, 1996, 10489874}. A total uncertainty factor (UF) of 100 was applied to the POD: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the chronic population adjusted dose (cPAD) was calculated to be 1 mg/kg/day {U.S. EPA, 2017c, 10532909}.

The EPA OPP HHRA reported that glyphosate is "not likely to be carcinogenic to humans" {U.S. EPA, 2017c, 10532909} according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

6.3.7.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.7.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-172 shows the comparison of the basis for the existing and potential MCLGs for glyphosate.

Table 6-172. Comparison of the Basis for Existing and Potential MCLGs for Glyphosate

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1989j, 10328171)	–	–	–	D	–	–	–	–	–	–
EPA (1989j, 10328171)	Biodynamics (1981, 11264445)	Increased incidence of kidney lesions in rats	–	–	0.1	20%	General Population	70 kg adult, 2 L/day	0.7	–
Relevant Health Assessment Identified in SYR 4										
EPA (2017c, 10532909)	–	–	–	N	–	–	–	–	–	–
EPA (2017c, 10532909)	Moxon (1996, 10489874)	Diarrhea in mice	–	–	1	20%	General Population	33.8 mL/ kg/day	–	6

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not applicable.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.3.7.5 SYR 4 Health Effects Conclusion

The existing NPDWR for glyphosate was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.1 mg/kg/day {U.S. EPA, 1989j, 10328171}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.7 mg/L {U.S. EPA, 1992g, 10587719} and designated a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1989j, 10328171}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2017c, 10532909} to derive the potential MCLG. Based on a PAD of 1.0 mg/kg/day, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 6 mg/L. Based on the analysis and conclusion presented in the EPA OPP HHRA, EPA updated the cancer classification to N, "not likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. EPA concluded that new health effects information supports raising the current MCLG of 0.7 mg/L to the potential MCLG of 6 mg/L.

6.3.8 Oxamyl (CAS# 23135-22-0 | DTXSID6021086)

6.3.8.1 Basis of the Existing MCLG

EPA published the current NPDWR for oxamyl on July 17, 1992, establishing both an MCLG and an MCL of 0.2 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.025 mg/kg/day and a cancer classification of E, "evidence of non-carcinogenicity for humans" {U.S. EPA, 1992q, 11311371}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.8.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for oxamyl that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-173).

Table 6-173. Most Recent OPP HHRA Identified for Oxamyl

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2017d, 10532947}[d]	**0.0026[e]**	**$BMDL_{10}$**	**McFarlane and Freestone (1999, 10522071)**	–	–	E[f]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; $BMDL_{10}$ = benchmark dose level at the 95% lower confidence limit on a 10% response; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference value expressed in mg/kg/day and refers to the acute population-adjusted dose (aPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Although this OPP assessment is labeled "draft," OPP considers it final at the time of publication in the Federal Register

[e] The EPA OPP HHRA states that the aPAD reported here is considered protective of chronic exposures because peak enzyme acetylcholinesterase (AChE) inhibition occurs quickly and recovers within hours.

[f] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

The health assessment selected for SYR 4 is the 2017 EPA OPP HHRA {U.S. EPA, 2017d, 10532947} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as oxamyl (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The EPA OPP HHRA identified a non-guideline acute oral toxicity study conducted in humans {McFarlane and Freestone, 1999, 10522071} as the critical study and source of the POD. In this study, 40 healthy human male volunteers aged 19–39 years (5 per dose group; 10 in control group) were each given a single oral dose of oxamyl in a gelatin capsule at doses of 0, 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 mg/kg body weight approximately five minutes after consumption of a "standard" breakfast. Blood was collected at several timepoints after dosing. A NOAEL of 0.06 mg/kg/day was identified from this study based on plasma and red blood cell (RBC) AChE inhibition observed within two hours of dosing {McFarlane and Freestone, 1999, 10522071}.

The EPA OPP HHRA generated BMD and BMDL estimates based on the RBC AChE inhibition data from this study. The resulting BMD_{10} was 0.083 mg/kg, which represents a 10% change in response, with a $BMDL_{10}$ of 0.069 mg/kg (lower bound of the confidence interval of the BMD_{10}). Peak inhibition occurred within 45–60 minutes, with recovery to normal RBC AChE three to four hours post-dosing. The $BMDL_{10}$ (0.069 mg/kg) was used as the POD to derive the acute population-adjusted dose (aPAD). A total uncertainty factory (UF) of 10 was applied to the POD for intraspecies variability. A FQPA safety factor of 2.64 was also applied for the extrapolation of adult data to be protective for infants and children (aged 0 to < 6 years), based on studies in rats that demonstrate that pups are more sensitive to oxamyl than adult rats {U.S. EPA, 2017d, 10532947}. After applying the total UF and FQPA safety factor, the oral aPAD for infants and children was calculated to be 0.0026 mg/kg/day.

The EPA OPP Draft HHRA reported that oxamyl is categorized as having "evidence of non-carcinogenicity for humans" according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on a lack of evidence of carcinogenicity in rats and mice {U.S. EPA, 2017d, 10532947}.

6.3.8.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.8.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-174 shows the comparison of the basis for the existing and potential MCLGs for oxamyl.

Table 6-174. Comparison of the Basis for the Existing and Potential MCLGs for Oxamyl

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992q, 11311371)	–	–	–	E	–	–	–	–	–	–
EPA (1992q, 11311371)	DuPont (1971, 11264451)	Decreased body weight gain and food consumption	–	–	0.025	20%	General Population	70 kg adult, 2 L/day	0.2	–
Relevant Health Assessment Identified in SYR 4										
EPA (2017d, 10532947)	–	–	–	E	–	–	–	–	–	–
EPA (2017d, 10532947)	McFarlane and Freestone (1999, 10522071)	Plasma and RBC AChE inhibition in humans	–	–	0.0026[d]	20%	Infants and Young Children[e]	60.9 mL/kg/day[f]	–	0.009

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).
[d] The infant and child aPAD is the selected RfV; no chronic oral RfV was derived. The EPA OPP HHRA states that peak AChE inhibition occurs quickly and recovers within hours, so repeated daily exposure does not result in increased inhibition of AChE, as the enzyme recovery is complete before the next acute exposure.
[e] Target population is infants and young children aged 0 to < 6 years {U.S. EPA, 2017d, 10532947}.
[f] Drinking water intakes for ages 0 to < 6 years, calculated using https://fcid.foodrisk.org/percentiles {JIFSAN, 2023, 10667059}.

6.3.8.5 SYR 4 Health Effects Conclusion

The existing NPDWR for oxamyl was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.025 mg/kg/day {U.S. EPA, 1992q, 11311371}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.2 mg/L and designated a cancer classification of E, "evidence of non-carcinogenicity for humans" {U.S. EPA, 1992q, 11311371}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2017d, 10532947} to derive the potential MCLG. Based on a PAD of 0.0026 mg/kg/day {McFarlane and Freestone, 1999, 10522071}, an adjusted DWI-BW ratio of 60.9 mL/kg/day for infants and young children aged 0 to < 6 years (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.009 mg/L. Based on the analysis and conclusion presented in this health assessment, the cancer classification was maintained as E, "evidence of non-carcinogenicity for humans," in accordance with EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. EPA concluded that, based on the available health effects information, there is potential to lower the current MCLG of 0.2 mg/L to the potential MCLG of 0.009 mg/L.

6.3.9 Picloram (CAS# 1918-02-1 | DTXSID1021160)

6.3.9.1 Basis of the Existing MCLG

EPA published the current NPDWR for picloram on July 17, 1992, establishing both an MCLG and MCL of 0.5 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.07 mg/kg/day and a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992r, 11311373}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} (see Table 3-1 for more information on cancer classification).

6.3.9.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for picloram that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected for SYR 4 (Table 6-175).

Table 6-175. Most Recent OPP HHRA Identified for Picloram

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2020b, 10533340}[d]	**0.2**	**NOAEL**	**Dow Chemical (1986, 10521738)**	–	–	E[e,f]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; NOAEL = no-observed-adverse-effect level; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day and refers to the chronic population-adjusted dose (cPAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] Although this OPP assessment is labeled "draft," OPP considers it final at the time of publication in the Federal Register.

[e] Based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}.

[f] EPA classified the manufacturing impurity hexachlorobenzene as a "probable human carcinogen" (Group B2).

The health assessment selected for SYR 4 is the 2020 EPA OPP HHRA {U.S. EPA, 2020b, 10533340} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as picloram (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The EPA OPP HHRA identified a combined chronic/carcinogenicity study in rats {Dow Chemical, 1986, 10521738} as the critical study and source of the POD. In this study, male and female Fisher 344 rats (n = 50/sex/dose) were fed picloram in the diet at 0, 20, 60, or 200 mg/kg/day for two years. A NOAEL of 20 mg/kg/day was determined based on the critical effects of increased size and altered staining properties of centrilobular hepatocytes and increased absolute and/or relative liver weights in rats exposed to ≥ 60 mg/kg/day. No neoplastic effects were observed at any dose level tested {Dow Chemical, 1986, 10521738}. The NOAEL of 20 mg/kg/day was used as the POD. A total uncertainty factor (UF) of 100 was applied: 10 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the chronic population-adjusted dose (cPAD) for all populations was calculated to be 0.2 mg/kg/day {U.S. EPA, 2020b, 10533340}.

The EPA OPP HHRA notes that picloram is categorized as having "evidence of non-carcinogenicity for humans" (Group E) according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on a lack of neoplastic effects in animals.

6.3.9.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.9.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-176 shows the comparison of the basis for the existing and potential MCLGs for picloram.

Table 6-176. Comparison of the Basis for the Existing and Potential MCLGs for Picloram

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992r, 11311373)	–	–		D	–	–	–	–	–	–
EPA (1992r, 11311373)	Dow Chemical (1982, 1311446)	Increased relative and absolute liver weights in dogs		–	0.07	20%	General Population	70 kg adult, 2 L/day	0.5	–
Relevant Health Assessment Identified in SYR 4										
EPA (2020b, 10533340)	–	–		E	–	–	–	–	–	–
EPA (2020b, 10533340)	Dow Chemical (1986, 10521738)	Increased size and altered staining properties of centrilobular hepatocytes and increased absolute and/or relative liver weights in rats		–	0.2	20%	General Population	33.8 mL/kg/ day	–	1

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided.
[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.
[b] Values expressed in mg/L unless otherwise specified.
[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

6.3.9.5 SYR 4 Health Effects Conclusion

The existing NPDWR for picloram was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.07 mg/kg/day {U.S. EPA, 1992r, 11311373}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), and an RSC of 20%, EPA set the MCLG at 0.5 mg/L and designated a cancer classification of D, "not classifiable as to human carcinogenicity" {U.S. EPA, 1992r, 11311373}, according to the 1986 EPA Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2020b, 10533340} to derive the potential MCLG. Based on a PAD of 0.2 mg/kg/day {U.S. EPA, 2020b, 10533340}, an adjusted DWI-BW ratio of 33.8 mL/kg/day for the general population (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 1 mg/L. Based on the analysis and conclusion presented in this health assessment, EPA updated the cancer classification to E, "evidence of non-carcinogenicity for humans" according to EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530} based on a lack of neoplastic effects in animals. EPA concluded that new health effects information supports raising the current MCLG of 0.5 mg/L to the potential MCLG of 1 mg/L.

6.3.10 Simazine (CAS# 122-34-9 | DTXSID4021268)

6.3.10.1 Basis of the Existing MCLG

EPA published the current NPDWR for simazine on July 17, 1992, establishing both an MCLG and MCL of 0.004 mg/L {U.S. EPA, 1992g, 10587719}. EPA based the MCLG on a reference dose of 0.005 mg/kg/day and a cancer classification of C, "possible human carcinogen" {U.S. EPA, 1992s, 11311374}, based on EPA's 1986 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 1986a, 199530}. At promulgation, simazine was classified as a Category II chemical due to limited evidence of carcinogenicity from drinking water and a risk management safety factor of 10 was applied {U.S. EPA, 1992g, 10587719} (see Table 3-1 for more information on cancer classification and application of a risk management safety factor).

6.3.10.2 Results of the SYR 4 Health Assessment Search

The following table shows the most recent final health assessment relevant to chronic toxicity available for simazine that was published prior to the cut-off date of November, 2020 from the EPA OPP. The OPP HHRA was selected (Table 6-177).

Table 6-177. Most Recent OPP HHRA Identified for Simazine

Health Assessment[a]	Oral Reference Value[b]	POD Type	Oral RfV Critical Study	Oral Cancer Slope Factor[c]	Oral CSF Critical Study	Cancer Descriptor
EPA OPP HHRA {U.S. EPA, 2018b, 10533123}	**0.073[d]**	**$BMDL_{1SD}$**	**Cooper et al. (2010, 10534153)[e]**	–	–	N[f]

Notes: POD = point of departure; RfV = reference value; CSF = cancer slope factor; $BMDL_{1SD}$ = benchmark dose level corresponding to a change in the mean response equal to one standard deviation from the control; dash (–) = not provided.

[a] Selected health assessment and chronic toxicity value bolded.

[b] Oral reference values expressed in mg/kg/day and refers to the population-adjusted dose (PAD).

[c] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified.

[d] A 4-day aPAD for females aged 13 to 49 years was used as the RfV, as this was the exposure duration that elicited a response in the critical study, and longer exposure durations did not lead to greater toxicity.

[e] This study was performed using atrazine, and assessed oral, dermal, and inhalation exposures. As noted in the EPA OPP HHRA, atrazine, propazine, and simazine have common metabolites, and EPA determined that they share a common neuroendocrine mechanism of toxicity and constitute the triazine common mechanism group.
[f] Based on EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}.

The health assessment selected for SYR 4 is the 2018 EPA OPP HHRA for Simazine {U.S. EPA, 2018b, 10533123} because the most recent EPA OPP HHRA is selected for pesticides with active registrations or tolerances, such as simazine (see Section 4.1.2.1 for the decision-logic that was applied for actively registered pesticides). The EPA OPP HHRA identified a subacute study on atrazine {Cooper, 2010, 10534153} as the critical study and source of the POD for simazine. Effects of atrazine exposure on regularly cycling female rats was examined over a period of four days (day of vaginal estrous through the day after proestrus) at doses of 0, 1.56, 3.12, 6.25, 12.5, 25, or 75 mg/kg/day. As noted in the EPA OPP HHRA, this study is considered relevant to simazine because simazine and atrazine have similar chemical structures and share a common mechanism of neuroendocrine toxicity. EPA assumed equal potency for neuroendocrine effects for simazine and atrazine. Further, atrazine was used for endpoint selection for simazine because it has a more extensive toxicological database and is well characterized for neuroendocrine toxicity. The selected critical study found a statistically significant attenuation of the pre-ovulatory luteinizing hormone (LH) surge at doses of ≥ 3.12 mg/kg/day atrazine {Cooper, 2010, 10534153}. EPA used BMD modeling to derive a $BMDL_{1SD}$ (BMD lower bound of the confidence limit) of 2.42 mg/kg/day based on this effect {U.S. EPA, 2018b, 10533123}.

The EPA OPP HHRA used a physiologically-based pharmacokinetic (PBPK) model to extrapolate the atrazine animal $BMDL_{1SD}$ to a toxicologically-relevant internal metric (i.e., the average TCT (total chlorotriazines) concentration in plasma). This model was parameterized to include growth from birth to adulthood for inhalation and dermal exposures. The PODs were derived for exposures to three human subpopulations, children (ages 6–12), youth (ages 13–19), and females (ages 13–49) of four days or longer, because four days is the duration after which decreased LH surge in rats was observed {Cooper et al., 2010, 10534153}. Longer exposure durations are not expected to result in greater toxicity. The model was further refined for simazine by using simazine-specific parameter values to derive a human POD. EPA subsequently used the lowest POD, 2.32 mg/kg/day for the most sensitive subpopulation, females (ages 13–49), as the basis to derive the RfV. A total uncertainty factor (UF) of 30 was applied to the POD: 3 for interspecies variability and 10 for intraspecies variability. After applying the total UF and a FQPA safety factor of 1, the 4-day population adjusted dose (PAD) for females (ages 13–49) was calculated to be 0.073 mg/kg/day for simazine {U.S. EPA, 2018b, 10533123}.

The EPA OPP HHRA reports that the HED CARC evaluated the carcinogenic potential of atrazine and the possibility that any mode of action which may be selected for atrazine would apply for simazine. Therefore, EPA categorized simazine as "not likely to be carcinogenic to humans" according to EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976} based on the weight of evidence conclusion that simazine is not genotoxic, and that the development of mammary and pituitary tumors seen in female Sprague-Dawley rats occurs through a similar mode of action as that of atrazine {U.S. EPA, 2018b, 10533123}.

6.3.10.3 SYR 4 Literature Search Results

The purpose of conducting literature searches for health effects information was to identify potential emerging issues and to characterize data gaps. To avoid duplicating efforts, OW did not conduct literature searches for active pesticides included in SYR 4 because OPP performs such searches for pesticides actively registered and regulated under FIFRA.

6.3.10.4 Comparison of Existing MCLG to SYR 4 Potential MCLG

Table 6-178 shows the comparison of the basis for the existing and potential MCLGs for simazine.

Table 6-178. Comparison of the Basis for Existing and Potential MCLGs for Simazine

Reference	Critical Study	Critical Effect	Oral Cancer Slope Factor[a]	Cancer Descriptor	Oral RfV[a]	Relative Source Contribution	Target Population	Exposure Factors	Existing NPDWR MCLG[b]	Potential MCLG[b,c]
Basis of Regulation										
EPA (1992s, 11311374)	McCormick et al. (1988, 11264475)	Rat mammary gland carcinomas	–	C[d]	–	–	–	–	–	–
EPA (1992s, 11311374)	McCormick et al. (1988, 11264475)	Depressed body weight gain, adverse effects on several hematological parameters	–	–	0.005	20%	General Population	70 kg adult, 2 L/day	0.004	–
Relevant Health Assessment Identified in SYR 4										
EPA (2018b, 10533123)	–	–	–	N	–	–	–	–	–	–
EPA (2018b, 10533123)	Cooper et al. (2010, 10534153)[e]	Attenuation of the LH surge in rats	–	–	0.073[f]	20%	Females aged 13–49 years[g]	35.6 mL/ kg/day[h]	–	0.4

Notes: RfV = reference value; NPDWR = National Primary Drinking Water Regulation; MCLG = maximum contaminant level goal; dash (–) = not provided; LH = luteinizing hormone.

[a] Cancer slope factors expressed in $(mg/kg/day)^{-1}$ unless otherwise specified; oral reference values expressed in mg/kg/day unless otherwise specified.

[b] Values expressed in mg/L unless otherwise specified.

[c] Potential MCLG was calculated using the 90th percentile drinking water intake (mL/kg/day).

[d] At rule promulgation, simazine was classified as Category II according to EPA's Cancer Categories Decision Tree. A risk management safety factor of 10 was applied in the calculation of the MCLG.

[e] This study was performed using atrazine and assessed oral, dermal, and inhalation exposures. As noted in the EPA OPP HHRA, atrazine, propazine, and simazine have common metabolites, and EPA determined they share a common neuroendocrine mechanism of toxicity and constitute the triazine common mechanism group.

[f] A 4-day PAD for females aged 13–49 years was used as the RfV as this was the exposure duration required to elicit a response in rats in the critical study, and longer exposure durations did not lead to greater toxicity.

[g] Target population is females aged 13–49 years as indicated in EPA (2018b, 10533123).

[h] Drinking water intakes for children aged 0–13 years were calculated using https://fcid.foodrisk.org/percentiles# {JIFSAN, 2023, 10667059}.

6.3.10.5 SYR 4 Health Effects Conclusion

The existing NPDWR for simazine was published on July 17, 1992 {U.S. EPA, 1992g, 10587719}. Based on an RfD of 0.005 mg/kg/day {U.S. EPA, 1992s, 11311374}, DWI and BW values for the general population (i.e., 2 L/day and 70 kg), an RSC of 20%, and application of a risk management safety factor of 10 EPA set the MCLG at 0.004 mg/L and designated simazine as a Category II carcinogen {U.S. EPA, 1992g, 10587719}. Following the SYR 4 health assessment search and selection protocols outlined in Section 4.1.2.1, EPA selected the most recent EPA OPP HHRA {U.S. EPA, 2018b, 10533123} to derive the potential MCLG. Based on a PAD of 0.073 mg/kg/day {U.S. EPA, 2018b, 10533123}, an adjusted DWI-BW ratio of 35.4 mL/kg/day for females of childbearing age (13–49 years) (see Section 4.2 for further information on target population selection), and an RSC of 20%, EPA calculated a potential MCLG of 0.4 mg/L. Based on the analysis and conclusion presented in this health assessment that the carcinogenic potential and mode of action selected for atrazine also applies for simazine, EPA updated the cancer classification for simazine to N, "not likely to be carcinogenic to humans," in accordance with EPA's 2005 Guidelines for Carcinogen Risk Assessment {U.S. EPA, 2005d, 10263976}. As a result of this conclusion, the risk management safety factor of 10 was removed when calculating the potential MCLG. EPA concluded that new health effects information supports raising the current MCLG of 0.004 mg/L to the potential MCLG of 0.4 mg/L.

7 Conclusions

The 1996 amendments to the SDWA require EPA to review every six years existing NPDWRs and determine which, if any, are appropriate for revision. Under the SYR 4, EPA has completed a health effects review of 73 water contaminants currently regulated under the SDWA. EPA identified 11 NPDWRs with recent, ongoing or pending regulatory actions or ongoing health assessments and deferred them from a detailed health effects review (see Section 3).

This review focused on the evaluation of the 62 List B chemicals to determine whether new information is available that could affect the MCLGs and perhaps the MCLs. For 33 of these chemicals, based on the analysis of the current information, no change to the MCLG is indicated at this time (see Table 5-1).

Based on this assessment, EPA identified 29 List B chemicals with health effects information that could potentially change the current MCLG. For 14 of the 29 chemicals, EPA identified health information supporting the potential to raise the MCLG. For the remaining 15 chemicals (in bold below), the agency concluded that there is potential for the MCLG to decrease based on the analysis of the available health effects information. The 29 chemicals are listed below:

1,2,4-Trichlorobenzene
1,1,1-Trichloroethane
1,1-Dichloroethylene
2,4 Dichlorophenoxy-acetic Acid (2,4-D)
Alachlor
Antimony
Atrazine
Barium
Beryllium
Cadmium
Carbofuran
cis-1,2-Dichloroethylene
Cyanide
Diquat
Endothall
Fluoride
Glyphosate
Hexachlorocyclopentadiene
Lindane
Methoxychlor
o – Dichlorobenzene (1,2-Dichlorobenzene)
Oxamyl
p – Dichlorobenzene (1,4-Dichlorobenzene)
Picloram
Selenium
Simazine
Styrene
Toluene
Xylenes (total)

The chemicals listed above were identified based on health effects only and independent of other considerations (e.g., analytical and occurrence data) that may influence the identification of contaminants for revision. For additional information on other considerations in determining if a revision is appropriate at this time, see the following support documents:

- EPA Protocol for the Fourth Review of Existing National Primary Drinking Water Regulations {U.S. EPA, 2024a, 11346388}
- Six-Year Review 4 Technical Support Document for Microbial Contaminant Regulations {U.S. EPA, 2024b, 11346389}.
- Analytical Feasibility Support Document for the Fourth Six-Year Review of National Primary Drinking Water Regulations {U.S. EPA, 2024c, 11346385}
- Occurrence Analysis for Potential Source Waters for the Fourth Six-Year Review of National Primary Drinking Water Regulations {U.S. EPA, 2024d, 11346386}

- The Analysis of Regulated Contaminant Occurrence Data from Public Water Systems in Support of the Fourth Six-Year Review of National Primary Drinking Water Regulations: Chemical Phase and Radionuclides Rules {U.S. EPA, 2024e, 11346390}

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Appendices

Appendix A Key Differences in Human Health Assessment Between the U.S. Environmental Protection Agency and Other Organizations Discussed in this Document

As part of the evaluation of the List B chemicals, assessments by several other regulatory bodies or authoritative organizations were reviewed, including assessments from the ATSDR, CalEPA, the WHO, HC, and NAS. To provide context to that review, key differences between the human health assessment methods of these other organizations and those of the U.S. Environmental Protection Agency (EPA) are summarized here.

ATSDR establishes oral minimal risk levels (MRLs for non-cancer endpoints for acute (1–14 days), intermediate (15–364 days), and chronic (365 days or more) exposure durations. MRLs for oral chronic exposure are derived using approaches similar to EPA's RfDs. However, ATSDR and EPA use different approaches when the database is limited to subchronic studies and no adequate chronic study is available. In such cases, EPA derives a chronic RfD from a subchronic study, incorporating an additional uncertainty factor to account for use of a subchronic study. ATSDR derives an intermediate duration MRL and it generally does not derive a chronic oral MRL by incorporating an additional uncertainty factor to account for using a less-than-lifetime study. ATSDR does not derive MRLs for cancer. Therefore, ATSDR does not perform quantitative cancer risk assessments or assign formal cancer classifications or descriptors, although an overall summary of the data pertaining to carcinogenic potential is provided. For cancer effects, ATSDR typically reports the cancer classifications developed by other authoritative sources such as the National Toxicology Program (NTP), EPA, and International Agency for Research on Cancer (IARC) in their toxicological profiles.

CalEPA establishes a Public Health Goal (PHG), which is a water concentration that is the state's equivalent to the MCLG. The PHG can be based on either cancer or noncancer endpoints. When the PHG is based on cancer endpoints, CalEPA estimates a cancer potency factor and then uses the potency factor to estimate the daily water intake that is equivalent to a 10^{-6} cancer risk, utilizing lifestage adjusted drinking water intake and drinking water equivalent exposures that include exposures from inhalation and dermal routes from bathing and showering. When the PHG is based on noncancer endpoints, the reference value, called Acceptable Daily Intake, may utilize a point of departure derived using EPA's BMD modeling. A total (maximum) uncertainty factor of 3,000 may be utilized, with intrahuman variability of up to 30× compared to 10× by EPA. The PHG for noncancer effects sometimes also includes a drinking water intake rate adjusted to lifestages and inhalation and dermal route exposures from bathing and showering, akin to EPA's relative source contribution (RSC).

WHO establishes a "guideline value," a drinking water concentration that is developed in a process analogous to that for the MCLG. However, WHO uses different default assumptions for estimating water concentration, including a 60 kg adult body weight, along with the traditional daily water consumption of 2 L/day and the default RSC of 20%. The guideline value can also address infant and child water consumption differences and changes to RSC as allowed by the data. WHO develops one guideline value that is based either on cancer or noncancer endpoints. For genotoxic carcinogens a value may be based on a concentration calculated to correspond to a cancer risk, usually 10^{-5}. WHO also states that member states can make adjustments by a factor of 10 above and below that 10^{-5} guideline value.

HC concludes that for substances with no threshold (i.e., mutagens and genotoxic carcinogens), it is assumed that there is some probability of harm to human health at any level of exposure. Health-based values for carcinogens are generally established on the basis of an estimation of lifetime cancer risk that would be sufficiently small so as to be "essentially negligible," which HC has defined in the context of drinking water guidelines as a range from one new cancer above background per 100,000 people to one

new cancer above background per 1,000,000 people (i.e., 10^{-5} to 10^{-6}) over a lifetime of 70 years. For non-carcinogens, an approach similar to EPA's RfD methodology is used {U.S. EPA, 2002d, 88824}. For calculating water concentrations, default values of 70 kg body weight, 1.5 L water intake per day, and an RSC of either 20% or a value based on actual exposure data are used. In the case of volatile compounds (both carcinogenic and non-carcinogenic), HC employs a multi-route exposure approach to estimate the relative contribution of the inhalation and dermal exposures during showering and bathing. Using this approach, liter-equivalent contributions are estimated for both the inhalation and dermal routes of exposure which are then added to the daily oral water intake to reflect an overall daily intake from all potential routes of exposure for drinking water.

Appendix B NTP Systematic Review of Scientific Research on Fluoride Exposure and Developmental Neurotoxicity

EPA is aware of animal toxicity and human epidemiology studies that assessed a potential association between developmental neurotoxicity and fluoride exposure in the published literature and, along with other U.S. health agencies, recognizes the need to review and analyze the studies in order to understand the potential developmental neurotoxicity effects of fluoride. For the history of the assessment of fluoride in SYR cycles 1–3, please see Appendix C of the Six-Year Review 3—Health Effects Assessment for Existing Chemical and Radionuclide National Primary Drinking Water Regulations—Summary Report {U.S. EPA, 2016c, 6557097}. During the SYR 4 assessment identification process (see Sections 4.1.1 and 4.1.2), the most recent final qualifying health assessment for fluoride that was published by the November 2020 cutoff date was the OW Dose Response Analysis for Noncancer Effects {U.S. EPA, 2010d, 10493692}. Therefore, this assessment {U.S. EPA, 2010d, 10493692} which developed an RfD based on severe dental fluorosis in children was used to derive a potential MCLG (see Section 6.1.20). The EPA {U.S. EPA, 2010d, 10493692} health assessment considered severe dental fluorosis to be an adverse effect based on the scientific review of EPA's standards for fluoride conducted by the National Research Council (NRC) that concluded that severe, but not moderate, dental fluorosis is an adverse health outcome {NRC, 2006, 11328274}. The available published literature on other health effect categories including neurotoxicity and behavior, reproduction and development, endocrine effects, and cancer were also reviewed in the EPA assessment {U.S. EPA, 2010d, 10493692}. Based on the review of the available literature at the time, EPA determined that the data for these other health effects after fluoride exposure were insufficient to support critical effect selection for the MCLG {U.S. EPA, 2010d, 10493692}.

EPA is aware of ongoing efforts by the National Toxicology Program (NTP) to conduct a systematic review and meta-analysis of the published literature on developmental neurotoxicity for fluoride in order to:

> "…evaluate the extent and quality of the evidence linking fluoride exposure to neurodevelopmental and cognitive effects in humans" {p. 667; NTP, 2023, 11328271}

A response to a reviewer comment in the NTP report states that:

> "The goal of the current, extensively revised monograph is to provide a comprehensive assessment of the scientific literature on fluoride as an important resource to inform its safe and appropriate use. The prepublication 2022 NTP Monograph includes a number of additional studies and provides the most complete and transparent critical assessment of the human epidemiological literature to date." {p. 42; NTP, 2023, 11328271}

However, it is important to point out that the NTP systematic review and meta-analysis are not intended to be health assessments that could be used to directly inform derivation of a potential MCLG because they will not include a chronic oral reference dose (RfD). As noted in Section 4.1.1, a qualifying health assessment is a final, peer-reviewed assessment that provides a toxicity value (i.e., a cancer slope factor and/or a noncancer oral RfD) and/or a cancer descriptor.

The NTP effort to evaluate the potential neurobehavioral effects associated with fluoride exposure is expected to provide an authoritative determination of the level and quality of evidence for developmental neurotoxicity after fluoride exposure to humans. In May 2023, NTP released the Draft NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review {NTP, 2023, 11328271; https://ntp.niehs.nih.gov/sites/default/files/2023-05/BSC_WG_Report_Final_Version_BSC_approved051623_508.pdf}. In this draft report, NTP review concludes that there is:

> "…moderate confidence, that higher fluoride exposure (e.g., represented by populations whose total fluoride exposure approximates or exceeds the World Health Organization Guidelines for Drinking-water Quality of 1.5 mg/L of fluoride) is consistently associated with lower IQ in children. More studies are needed to fully understand the potential for lower fluoride exposure to affect children's IQ." {p. 13; NTP, 2023, 11328271}

While EPA has reviewed the NTP Board of Scientific Counselors (BSC) Working Group's final report {NTP, 2023, 11328271}, it is important to point out that the NTP Director has not made a final decision about the report's conclusions and has not formally released a final report (https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/ongoing/fluoride).

Following publication of the final NTP report, EPA will consider the systematic review and meta-analysis conclusions regarding developmental neurotoxicity to inform the agency's future development of a health effects assessment for fluoride at that time.

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Appendix C Search Date Limits and Synonyms

C.1 Search Strings

C.1.1 PubMed

The following search strategy was used in PubMed® unless otherwise specified. The first set of the search string is the list of synonyms curated by utilizing the U.S. Environmental Protection Agency (EPA) CompTox Chemicals Dashboard and ChemID*Plus,* and the second set of the search string is pre-curated topic-specific query that limits the search to the PubMed toxicology subset (listed in Table C-1).

Table C-1. PubMed® Search Strategy

Set	Search Strategy
Set 1 (Synonyms)	The list of synonyms for each chemical are provided in Appendix C.
Set 2 (Tox Filter)	AND ("Toxicol Sci"[TA] OR (drug-induced abnormalities OR occupational accidents OR adverse drug reaction reporting systems OR Drug-Induced Akathisia OR Amino Acids, Peptides, and Proteins/adverse effects[Mesh] OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Background Radiation OR biohazard release OR Biological Factors/adverse effects[Mesh] OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR chemical burns OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR Chemical and Drug Induced Liver Injury OR chemical hazard release OR chemical terrorism OR Chemically-Induced Disorders OR Climate Change OR Clin Toxicol Phila[TA] OR Colony Collapse OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Digestive System Diseases/chemically induced[Mesh] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Drug Interactions OR Drug Recalls OR drug therapy/adverse effects[Mesh] OR Drug-Induced Dyskinesia OR ecotox* OR Ecotoxicology OR Endocrine System Diseases/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Environmental Restoration and Remediation OR Enzymes and Coenzymes/adverse effects[Mesh] OR Extreme Environments OR Eye Diseases/chemically induced[Mesh] OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR Fetal Alcohol Spectrum Disorders OR food and beverages/adverse effects[Mesh] OR forensic toxicology OR Genetic Phenomena/drug effects[Mesh] OR Global Warming OR hazardous substances OR Hemic and Lymphatic Diseases/chemically induced[Mesh] OR hepatotox* OR Heterocyclic Compounds/adverse effects[Mesh] OR Hormones, Hormone Substitutes, and Hormone Antagonists/adverse effects[Mesh] OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Inorganic Chemicals/adverse effects[Mesh] OR Integumentary System Physiological Phenomena/drug effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR LC50 OR Lipids/adverse effects[Mesh] OR Macromolecular Substances/adverse effects[Mesh] OR Male Urogenital Diseases/chemically induced[Mesh] OR manufactured materials/adverse effects[Mesh] OR Material Safety Data Sheets OR mental disorders/chemically induced[Mesh] OR Musculoskeletal Diseases/chemically induced[Mesh] OR mutagen* OR mutagenesis OR nanostructures OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nuclear Power Plants OR Nucleic Acids, Nucleotides, and Nucleosides/adverse effects[Mesh] OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Ocular Physiological Phenomena/drug

Set	Search Strategy
	effects[Mesh] OR Organic Chemicals/adverse effects[Mesh] OR Otorhinolaryngologic Diseases/chemically induced[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR persian gulf syndrome OR pesticides/toxicity[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR Phytochemicals/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR toxic plants OR poison* OR poisoning OR Polycyclic Compounds/adverse effects[Mesh] OR substance-induced psychoses OR radiation injuries OR Radiation Monitoring OR radiation-induced abnormalities OR Radioactive Hazard Release OR Radioactive Pollutants OR radiotherapy/adverse effects[Mesh] OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR Respiratory Tract Diseases/chemically induced[Mesh] OR Safety-Based Drug Withdrawals OR Skin and Connective Tissue Diseases/chemically induced[Mesh] OR Stomatognathic Diseases/chemically induced[Mesh] OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Drug Therapeutic Index OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR Toxicology[TA] OR toxif* OR toxig* OR Toxin-Antitoxin Systems OR venoms/toxicity[Mesh]))
Limit: Language	AND (English[lang])

C.2 Web of Science

The following search strategy was used in Web of Science unless otherwise specified. The first set of the search string is the list of synonyms curated by utilizing the EPA CompTox Chemicals Dashboard and ChemID*Plus,* and the second set of the search string is the toxicology filter developed from the relevant research areas in within the biomedicine and life science and categories (listed in Table C-2).

Table C-2. Web of Science Search Strategy

Set	Search Strategy
Set 1 (Synonyms)	The list of synonyms for each chemical are provided in Appendix C.
Set 2 (Tox Filter)	AND ((“adverse effects” AND (“Amino Acids, Peptides, and Proteins “ OR “Biological Factors “ OR “Biomedical Materials” OR “Dental Materials” OR Carbohydrates OR “Chemical Actions” OR “Chemical Uses” OR “Complex Mixtures” OR “drug therapy” OR “Environment Health” OR “Public Health” OR Enzymes OR Coenzymes OR food OR beverages OR Hormones OR “Hormone Substitutes” OR “Hormone Antagonists” OR “Heterocyclic Compounds” OR “household products” OR Lipids OR “Macromolecular Substances” OR “Nucleic Acids” OR Nucleotides OR Nucleosides “Pharmaceutical Preparations” OR Phytochemicals OR “Polycyclic Compounds” OR radiotherapy)) OR ((“chemically induced” OR “chemical induced”) AND (“Animal Diseases” OR “Cardiovascular Diseases” OR “Congenital Diseases” OR “Congenital Abnormalities” OR “Hereditary Diseases” OR “Hereditary Abnormalities” OR “Neonatal Diseases” OR “Neonatal Abnormalities” OR “Digestive System Diseases” OR “Disorders of Environmental Origin” OR “Environmental Disorders” OR “Endocrine System Diseases” OR “Eye Diseases” OR “Urogenital Diseases” OR “Pregnancy Complications” OR “Hemic Diseases” OR “Lymphatic Diseases” OR “Immune System Diseases” OR “Immune Diseases” OR “mental disorders” OR “Musculoskeletal Diseases” OR “Neoplasms” OR “Cancer” OR “Nervous System Diseases” OR “Nutritional Diseases” OR “Metabolic Diseases” OR “Otorhinolaryngologic Diseases” OR “Pathological Conditions” OR “Pathological Signs” OR “Pathological Symptoms” OR “Respiratory Tract Diseases” OR “Stomatognathic Diseases” OR “Skin Diseases” OR “Connective Tissue Diseases” OR “Liver injury”)) OR ((“drug effects” OR “drug induced”) AND (“birth weight” OR “Genetic Phenomena” OR

Set	Search Strategy
	"Integumentary System Physiological Phenomena" OR "Ocular Physiological Phenomena" OR "Reproductive Physiological Phenomena" OR "Urinary Physiological Phenomena" OR "liver injury")) OR "drug-induced abnormalities" OR "occupational accidents" OR "adverse drug reaction reporting systems" OR "Drug-Induced Akathisia" OR "biohazard release" OR "chemical burns" OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR "chemical hazard release" OR "chemical terrorism" OR "Chemically-Induced Disorders" OR "chemical induced disorders" OR "Colony Collapse" OR "Drug Interactions" OR "Drug Recalls" OR "Drug-Induced Dyskinesia" OR ecotox* OR Ecotoxicology OR "Environmental Health" OR "environmental illness" OR "environmental monitoring" OR "environmental pollutants" OR "environmental pollution" OR "Environmental Restoration" OR "Environmental Remediation" OR "Fetal Alcohol Spectrum" OR "forensic toxicology" OR "hazardous substances" OR hepatotox* OR immunotox* OR "Metabolic Inactivation" OR "LC50" OR "Material Safety Data Sheets" OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR "occupational diseases" OR "persian gulf syndrome" OR Pesticides OR poison* OR poisoning OR "substance-induced psychoses" OR terata* OR terato* OR Teratogenesis OR "Toxic Actions" OR toxic OR "toxicity tests" OR Toxicokinetics OR "Toxicological Phenomena" OR toxicology OR toxif* OR toxig* OR "Toxin-Antitoxin Systems")

Web of Science searches were limited to the following research areas within the biomedicine and life science categories (listed in Table C-3).

Table C-3. Relevant Research Areas in Web of Science

Research Areas
Allergy
Anatomy & Morphology
Audiology & Speech-Language Pathology
Behavioral Sciences
Cardiovascular System & Cardiology
Critical Care Medicine
Dentistry, Oral Surgery & Medicine
Dermatology
Developmental Biology
Emergency Medicine
Endocrinology & Metabolism
Gastroenterology & Hepatology
General & Internal Medicine
Genetics & Heredity
Geriatrics & Gerontology
Hematology
Immunology
Infectious Diseases
Neurosciences & Neurology
Nutrition & Dietetics
Obstetrics & Gynecology
Oncology
Ophthalmology
Orthopedics
Otorhinolaryngology
Pathology
Physiology
Psychiatry
Public, Environmental & Occupational Health
Reproductive Biology
Respiratory System
Rheumatology
Toxicology
Urology & Nephrology

C.3 Search Strategies for Non-TSCA Chemicals

C.3.1 Acrylamide (CAS# 79-06-1 | DTXSID5020027)

A standard literature search was conducted for acrylamide using the search parameters shown in Table C-4 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-4. Set #1 of Search Strategy for Acrylamide

Chemical	Acrylamide
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/08/22
Synonyms	("2-Propenamide"[tiab] OR "79-06-1"[rn] OR "79-06-1"[tiab] OR "Acrylamide"[mh] OR "Acrylamide"[tiab] OR "Prop-2-enamide"[tiab] OR "2-Propene amide"[tiab] OR "Acrylamid"[tiab] OR "Acrylamide monomer"[tiab] OR "Acrylic acid amide"[tiab] OR "Acrylic amide"[tiab] OR "Bio-Acrylamide 50"[tiab] OR "Ethylenecarboxamide"[tiab] OR "NSC 7785"[tiab] OR "Propenamide"[tiab] OR "UN 2074"[tiab] OR "UN3426"[tiab] OR "Vinyl amide"[tiab] OR "DTXSID5020027"[tiab] OR "4-02-00-01471 (Beilstein Handbook Reference)"[tiab] OR "AAM"[tiab] OR "Acrylagel"[tiab] OR "AI3-04119"[tiab] OR "Amresco Acryl-40"[tiab] OR "BRN 0605349"[tiab] OR "CCRIS 7"[tiab] OR "EC 201-173-7"[tiab] OR "EINECS 201-173-7"[tiab] OR "HSDB 191"[tiab] OR "Propeneamide"[tiab] OR "Propenoic acid amide"[tiab] OR "RCRA waste number U007"[tiab])

C.3.2 Antimony (CAS# 7440-36-0 | DTXSID5023879)

A standard literature search was conducted for antimony using the search parameters shown in Table C-5 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-5. Set #1 of Search Strategy for Antimony

Chemical	Antimony
Assessment for Date Limit	ATSDR (2019a, 10536389)
Search Date Limit	01/01/17
Search Date	01/24/22
Synonyms	("7440-36-0"[rn] OR "Antimony"[tiab] OR "Antimony black"[tiab] OR "Antimony element"[tiab] OR "C.I. 77050"[tiab] OR "Stibium"[tiab] OR "ANTIMONY METAL"[tiab] OR "UN 2871"[tiab] OR "DTXSID5023879"[tiab] OR "Antimony, elemental"[tiab] OR "Antimony, metallic"[tiab] OR "Antimony, regulus"[tiab] OR "CI 77050"[tiab] OR "EC 231-146-5"[tiab] OR "EINECS 231-146-5"[tiab] OR "HSDB 508"[tiab] OR "Regulus of antimony"[tiab] OR "Stibium metallicum"[tiab] OR "UNII-9IT35J3UV3"[tiab] OR "Antimony"[mh] OR "7440-36-0"[tiab])

C.3.3 Barium (CAS# 7440-39-3 | DTXSID8023894)

Two literature searches were conducted for barium. One search was the standard literature search using the search parameters shown in Table C-6 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-6. Set #1 of Search Strategy for Barium

Chemical	Barium
Assessment for Date Limit	HC (2020a, 10529367)
Search Date Limit	01/01/19
Search Date	03/23/22
Synonyms	("7440-39-3"[RN] OR "Barium"[TIAB] OR "Barium and Compounds"[TIAB] OR "Barium and soluble compounds"[TIAB] OR "Barium element"[TIAB] OR "BARIUM METAL"[TIAB] OR "UN 1400"[TIAB] OR "UN 1854"[TIAB] OR "DTXSID8023894"[TIAB] OR "Barium"[Mesh] OR "Barium, elemental"[TIAB] OR "EINECS 231-149-1"[TIAB] OR "HSDB 4481"[TIAB] OR "UNII-24GP945V5T"[TIAB] OR "7440-39-3"[TIAB] OR "Barium ion"[TIAB])

The other search was a targeted literature search focused on developmental and reproductive toxicity, covering the time between the ATSDR Toxicological Profile {ATSDR 2007a, 669580} and the HC GDWQ (2020a, 10529367), spanning from January 2007 to January 2019. The search parameters and toxicology filters for PubMed® and Web of Science shown in Table C-7 and Table C-8, respectively.

Table C-7. Set #1 and Set #2 of Developmental and Reproductive Toxicity Search Strategy for Barium in PubMed

Chemical	Barium
Assessment for Date Limit	ATSDR (2007a, 669580) and HC (2020a, 10529367)
Search Date Limit	01/01/2019
Search Date	03/23/22
Set #1 (Synonyms)	("7440-39-3"[RN] OR "Barium"[TIAB] OR "Barium and Compounds"[TIAB] OR "Barium and soluble compounds"[TIAB] OR "Barium element"[TIAB] OR "BARIUM METAL"[TIAB] OR "UN 1400"[TIAB] OR "UN 1854"[TIAB] OR "DTXSID8023894"[TIAB] OR "Barium"[Mesh] OR "Barium, elemental"[TIAB] OR "EINECS 231-149-1"[TIAB] OR "HSDB 4481"[TIAB] OR "UNII-24GP945V5T"[TIAB] OR "7440-39-3"[TIAB] OR "Barium ion"[TIAB])
Set #2 (Filter)	AND ((abnormalities, drug-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR ((abnormalities, multiple/chemically induced [mh] OR abnormalities, multiple/epidemiology [mh] OR abnormalities, multiple/etiology[mh] OR abnormalities, multiple/genetics [mh] OR abnormalities, multiple/pathology [mh]) AND (pregnancy [mh] OR fetus [mh])) OR (abnormalities, radiation-induced [mh] AND (fetus [mh] or pregnancy [mh])) OR Birth Defects Res B Dev Reprod Toxicol [TA] OR birth weight/drug effects [mh] OR birth weight/radiation effects [mh] OR breast feeding/drug effects [mh] OR (cardiovascular abnormalities/chemically induced [mh] AND fetus [mh]) OR (cardiovascular abnormalities/etiology [mh] AND fetus [mh]) OR (cocaine[mh] AND (fetus [mh] or pregnancy [mh])) OR (congenital abnormalities [mh] AND (fetus [mh] or pregnancy [mh])) OR (dna damage [mh] AND (pregnancy [mh] OR fetus [mh])) OR embryo/drug effects [mh] OR embryo/radiation effects [mh] OR embryo loss/chemically induced [mh] OR embryonic and fetal development/drug effects [mh] OR embryonic and fetal development/radiation effects [mh] OR embryonic structures/drug effects [mh] OR embryonic structures/pathology [mh] OR embryonic structures/radiation effects [mh] OR (environmental exposure[mh] AND (pregnancy [mh] OR fetus [mh])) OR fertility/drug effects [mh] OR fertility/radiation effects [mh] OR fetal death/chemically induced [mh] OR fetal death/etiology [mh] OR fetal death/genetics [mh] OR fetal death/pathology [mh] OR fetal diseases/chemically induced [mh] OR fetal diseases/etiology [mh] OR fetal diseases/genetics [mh] OR fetal growth retardation/etiology [mh] OR fetal growth retardation/chemically induced [mh] OR fetal resorption/chemically induced [mh] OR fetal resorption/etiology [mh] OR fetal resorption/genetics [mh] OR fetus/abnormalities [mh] OR fetus/drug effects [mh] OR fetus/radiation effects [mh] OR (fetus*[tw] AND expos*[tw]) OR (genetic

Chemical	Barium
	diseases, inborn/Chemically induced [mh] AND (fetus [mh] OR pregnancy [mh])) OR germ cells/drug effects [mh] OR germ cells/radiation effects [mh] OR (hazardous substances [mh] AND (fetus [mh] or pregnancy [mh])) OR lactation/drug effects [mh] OR lactation/radiation effects [mh] OR (lead [mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR maternal exposure [mh] OR maternal-fetal exchange/genetics [mh] OR maternal-fetal exchange/drug effects [mh] OR maternal-fetal exchange/radiation effects [mh] OR (mutagens [mh] AND (pregnancy [mh] OR fetus [mh])) OR paternal exposure [mh] OR placenta diseases/chemically induced [mh] OR placenta diseases/etiology [mh] OR placenta/abnormalities [mh] OR placenta/drug effects [mh] OR placenta/radiation effects [mh] OR pregnancy Complications, Infectious/epidemiology [mh] OR pregnancy Complications/chemically induced [mh] OR pregnancy outcome/genetics [mh] OR (prenatal*[tw] AND expos*[tw]) OR prenatal exposure delayed effects [mh] OR (protein deficiency[mh:noexp] AND (fetus [mh] or pregnancy [mh])) OR reproduction/drug effects [mh:noexp] OR reproduction/radiation effects [mh] OR rubella/congenital[mh:noexp] OR rubella syndrome, congenital/etiology[mh:noexp] OR (teratogens [mh] AND (pregnancy [mh] OR fetus [mh])) OR Teratology [Journal] OR teratology [mh] OR testis/drug effects [mh] OR testis/radiation effects [mh]) OR Diet*[TIAB] OR ("Attention deficit/hyperactivity disorder"[TIAB] OR "Autism spectrum disorders"[TIAB] OR "Birth defects"[TIAB] OR "Cerebral palsy"[TIAB] OR "Child development"[TIAB] OR "Developmental delay"[TIAB] OR "Developmental disabilities"[TIAB] OR "Developmental disorders"[TIAB] OR "developmental health"[TIAB] OR "Endometriosis"[TIAB] OR "Erectile dysfunction"[TIAB] OR "Human Development"[Mesh] OR "human development"[TIAB] OR "Impotence"[TIAB] OR "Infant mortality"[TIAB] OR "Infertility"[TIAB] OR "Intellectual disability"[TIAB] OR "Language impairment"[TIAB] OR "Learning disability"[TIAB] OR "Low birth weight"[TIAB] OR "Low sperm count"[TIAB] OR "Menstrual disorders"[TIAB] OR "Neurodevelopmental disorders"[TIAB] OR "Polycystic ovary syndrome"[TIAB] OR "Preterm birth"[TIAB] OR "Reduced fertility"[TIAB] OR "Reproductive Health"[Mesh] OR "reproductive health"[TIAB] OR "Speech impairment"[TIAB] OR "Uterine fibroids"[TIAB] OR "Reproductive Health"[TA] OR "Human Reproduction"[TA] OR "Child Development"[TA] OR "JAMA Pediatrics"[TA] OR "Developmental Review"[TA] OR "ototoxicity"[TIAB] OR "hearing loss"[TIAB] OR "Hearing Loss"[Mesh] OR "tinnitus"[TIAB] OR "Tinnitus"[Mesh] OR "hearing disorders"[TIAB] OR "deaess"[TIAB] OR "vestibulotoxicity"[TIAB] OR "vestibular toxicity"[TIAB] OR "auditory toxicity"[TIAB] OR "American Journal of Audiology"[TA] OR "Seminars in Hearing"[TA] OR "Audiology and Neuro-Otology"[TA] OR "Hearing Research"[TA] OR "Neurotoxicology and Teratology"[TA] OR "Neurotoxicology"[TA])
Limit: Language	AND (English[lang])

Table C-8. Set #1 and Set #2 of Developmental and Reproductive Toxicity Search Strategy for Barium in WoS

Chemical	Barium
Assessment for Date Limit	ATSDR (2007a, 669580) and HC (2020a, 10529367)
Search Date Limit	01/01/2010
Search Date	12/31/2014
Set #1 (Synonyms)	("7440-39-3" OR "Barium" OR "Barium and Compounds" OR "Barium and soluble compounds" OR "Barium element" OR "BARIUM METAL" OR "UN 1400" OR "UN 1854" OR "DTXSID8023894" OR "Barium" OR "Barium, elemental" OR "EINECS 231-149-1" OR "HSDB 4481" OR "UNII-24GP945V5T" OR “Barium ion”)
Set #2 (Filter)	AND (((fetus OR pregnancy) AND (abnormalities AND (“drug induced” OR “chemically induced” OR “radiation induced” OR epidemiology OR etiology OR genetics OR pathology OR congenital))) OR (“inborn genetic diseases” AND “chemically induced”) OR (lactation AND (“drug effects” OR “radiation effects”)) OR (“breast feeding” AND “drug effects”) OR ((“cardiovascular abnormalities”

Chemical	Barium
	AND fetus) AND (“chemically induced” OR etiology)) OR ((embryo OR “embryonic and fetal development”) AND (“drug effects” OR “radiation effects”)) OR (“embryo loss” AND “chemically induced”) OR (“embryonic structures” AND (“drug effects” OR pathology OR “radiation effects”)) OR (fertility AND (“drug effects” OR “radiation effects”)) OR (“fetal death” AND (“chemically induced” OR etiology OR genetics OR pathology)) OR ((“fetal diseases” OR “fetal resorption”) AND (“chemically induced” OR etiology OR genetics)) OR (“fetal growth retardation” AND (etiology OR “chemically induced”)) OR (fetus AND (abnormalities OR “drug effects” OR “radiation effects”)) OR ((fetus* OR prenatal*) AND expos*) OR (“prenatal exposure” AND “delayed effects”) OR ((“germ cells” OR reproduction OR testis OR “birth weight”) AND (“drug effects” OR “radiation effects”)) OR “paternal exposure” OR “maternal exposure” OR (“maternal-fetal exchange” AND (genetics OR “drug effects” OR “radiation effects”)) OR (“placenta diseases” AND (“chemically induced” OR etiology)) OR (placenta AND (abnormalities OR “drug effects” OR “radiation effects”)) OR (“infectious pregnancy complications” AND epidemiology) OR (“pregnancy complications” AND “chemically induced”) OR (“pregnancy outcome” AND genetics) OR (rubella AND congenital) OR (“congenital rubella syndrome” AND etiology) OR “DNA damage” OR “environmental exposure” OR “hazardous substances” OR mutagens OR “protein deficiency” OR teratogens OR cocaine OR lead OR teratology OR Diet* OR ("Attention deficit/hyperactivity disorder" OR "Autism spectrum disorders" OR "Birth defects" OR "Cerebral palsy" OR "Child development" OR "Developmental delay" OR "Developmental disabilities" OR "Developmental disorders" OR "developmental health" OR "Endometriosis" OR "Erectile dysfunction" OR "human development" OR "Impotence" OR "Infant mortality" OR "Infertility" OR "Intellectual disability" OR "Language impairment" OR "Learning disability" OR "Low birth weight" OR "Low sperm count" OR "Menstrual disorders" OR "Neurodevelopmental disorders" OR "Polycystic ovary syndrome" OR "Preterm birth" OR "Reduced fertility" OR "reproductive health" OR "Speech impairment" OR "Uterine fibroids" OR "ototoxicity" OR "hearing loss" OR "tinnitus" OR "hearing disorders" OR "deafness" OR "vestibulotoxicity" OR "vestibular toxicity" OR "auditory toxicity"))

C.3.4 Benzene (CAS# 71-43-2 | DTXSID3039242)

A standard literature search was conducted for benzene using the search parameters shown in Table C-9 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-9. Set #1 of Search Strategy for Benzene

Chemical	Benzene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/04/22
Synonyms	("71-43-2"[rn] OR "71-43-2"[tiab] OR "DTXSID3039242"[tiab] OR "Benzene"[tiab] OR "1,3,5-Cyclohexatriene"[tiab] OR "[6]Annulene"[tiab] OR "Benceno"[tiab] OR "benceno, puro"[tiab] OR "Benzole"[tiab] OR "Coal naphtha"[tiab] OR "Cyclohexatriene"[tiab] OR "NSC 67315"[tiab] OR "Phenyl hydride"[tiab] OR "Pyrobenzol"[tiab] OR "Pyrobenzole"[tiab] OR "UN 1114"[tiab] OR "(6)Annulene"[tiab] OR "AI3-00808"[tiab] OR "Benzin"[tiab] OR "Benzin (Obs.)"[tiab] OR "Benzine"[tiab] OR "Benzine (Obs.)"[tiab] OR "Benzol"[tiab] OR "Benzol 90"[tiab] OR "Benzolene"[tiab] OR "Bicarburet of hydrogen"[tiab] OR "Carbon oil"[tiab] OR "Caswell No. 077"[tiab] OR "CCRIS 70"[tiab] OR "EC 200-753-7"[tiab] OR "EINECS 200-753-7"[tiab] OR "EPA Pesticide Chemical Code 008801"[tiab] OR "Fenzen"[tiab] OR "HSDB 35"[tiab] OR "Mineral naphtha"[tiab] OR "Motor benzol"[tiab] OR "NCI-C55276"[tiab] OR "Nitration benzene"[tiab] OR "Phene"[tiab] OR "Polystream"[tiab] OR "RCRA waste number U019"[tiab] OR "UNII-J64922108F"[tiab] OR "Benzene"[mh])

C.3.5 Benzo(a)pyrene (CAS# 50-32-8 | DTXSID2020139)

A standard literature search was conducted for benzo(a)pyrene using the search parameters shown in Table C-10 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-10. Set #1 of Search Strategy for Benzo(a)pyrene

Chemical	Benzo(a)pyrene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/08/22
Synonyms	("DTXSID2020139"[tiab] OR "50-32-8"[tiab] OR "50-32-8"[rn] OR "Benzo(a)pyrene"[tiab] OR "Benzo(a)pyrene"[mh] OR "Benzo[a]pyrene"[tiab] OR "Benzo[pqr]tetraphene"[tiab] OR "3,4-Benz[a]pyrene"[tiab] OR "3,4-Benzopyrene"[tiab] OR "3,4-Benzpyrene"[tiab] OR "6,7-Benzopyrene"[tiab] OR "Benz(a)pyren"[tiab] OR "Benz(a)pyrene"[tiab] OR "Benz[a]pyrene"[tiab] OR "Benzo[def]chrysen"[tiab] OR "Benzo[d,e,f]chrysene"[tiab] OR "Benzo[def]chrysene"[tiab] OR "benzo[def]criseno"[tiab] OR "NSC 21914"[tiab] OR "1,2-Benzpyrene"[tiab] OR "3,4-Benz(a)pyrene"[tiab] OR "3,4-Benzo(a)pyrene"[tiab] OR "3,4-BP"[tiab] OR "4,5-Benzpyrene"[tiab] OR "AI3-50461"[tiab] OR "B(a)P"[tiab] OR "Benzo(d,e,f)chrysene"[tiab] OR "CCRIS 76"[tiab] OR "EINECS 200-028-5"[tiab] OR "HSDB 2554"[tiab] OR "RCRA waste number U022"[tiab] OR "UNII-3417WMA06D"[tiab])

C.3.6 Beryllium (CAS# 7440-41-7 | DTXSID4023913)

A standard literature search was conducted for beryllium using the search parameters shown in Table C-11 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-11. Set #1 of Search Strategy for Beryllium

Chemical	Beryllium
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/23/22
Synonyms	("7440-41-7"[rn] OR "7440-41-7"[tiab] OR "Beryllium"[mh] OR "Beryllium"[tiab] OR "Beryllium and Compounds"[tiab] OR "Beryllium-9"[tiab] OR "Beryllium atom"[tiab] OR "Beryllium element"[tiab] OR "Glucinium"[tiab] OR "UN 1567"[tiab] OR "DTXSID4023913"[tiab] OR "Beryllium, elemental"[tiab] OR "Beryllium dust"[tiab] OR "Beryllium metal"[tiab] OR "Beryllium metallic"[tiab] OR "Beryllium, metal powder"[tiab] OR "CCRIS 81"[tiab] OR "EC 231-150-7"[tiab] OR "EINECS 231-150-7"[tiab] OR "Glucinum"[tiab] OR "HSDB 512"[tiab] OR "RCRA waste number P015"[tiab] OR "UNII-OW5102UV6N"[tiab])

C.3.7 Cadmium (CAS# 7440-43-9 | DTXSID1023940)

A standard literature search was conducted for cadmium using the search parameters shown in Table C-12 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-12. Set #1 of Search Strategy for Cadmium

Chemical	Cadmium
Assessment for Date Limit	HC (2020b, 10586919)
Search Date Limit	07/01/19
Search Date	03/04/22
Synonyms	("7440-43-9"[rn] OR "Cadmium"[mh] OR "7440-43-9"[tiab] OR "Cadmium"[tiab] OR "cadmium (non-pyrophoric)"[tiab] OR "cadmium (pyrophoric)"[tiab] OR "C.I. 77180"[tiab] OR "UN 2570"[tiab] OR "Cadimium"[tiab] OR "CADMIUM BLUE"[tiab] OR "48Cd"[tiab] OR "Colloidal cadmium"[tiab] OR "EINECS 231-152-8"[tiab] OR "UNII-00BH33GNGH"[tiab] OR "DTXSID1023940"[tiab] OR "C I 77180"[tiab] OR "CCRIS 112"[tiab] OR "EC 231-152-8"[tiab])

C.3.8 Chlordane (CAS# 57-74-9 | DTXSID7020267)

A standard literature search was conducted for chlordane using the search parameters shown in Table C-13 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-13. Set #1 of Search Strategy for Chlordane

Chemical	Chlordane
Assessment for Date Limit	ATSDR (1994, 1065240)
Search Date Limit	04/01/16
Search Date	03/10/22
Synonyms	("DTXSID7020267"[tiab] OR "57-74-9"[rn] OR "57-74-9"[tiab] OR "1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-endomethyleneindane"[tiab] OR "1,2,4,5,6,7,10,10-Octachloro-4,7,8,9-tetrahydro-4,7-methyleneindane"[tiab] OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoindene"[tiab] OR "1,2,4,5,6,7,8,8-Octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane"[tiab] OR "4,7-Methano-1H-indene, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-"[tiab] OR "4,7-Methanoindan, 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-"[tiab] OR "57-74-9"[tiab] OR "CD 68"[tiab] OR "Chlordan"[tiab] OR "Chlordane"[tiab] OR "Chlorindan"[tiab] OR "Cortilan-neu"[tiab] OR "Dowchlor"[tiab] OR "ENT 9932"[tiab] OR "HCS 3260"[tiab] OR "M 140"[tiab] OR "NSC 8931"[tiab] OR "Octachloro-4,7-methanotetrahydroindane"[tiab] OR "Oktaterr"[tiab] OR "Tat Chlor 4"[tiab] OR "Toxichlor"[tiab] OR "Chordane"[tiab] OR "1,2,4,5,6,7,8,8-Octachloor-3a,4,7,7a-tetrahydro-4,7-endo-methano-indaan"[tiab] OR "1,2,4,5,6,7,8,8-Octachlor-3a,4,7,7a-tetrahydro-4,7-endo-methano-indan"[tiab] OR "1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene"[tiab] OR "1,2,4,5,6,7,8,8-Ottochloro-3a,4,7,7a-tetraidro-4,7-endo-metano-indano"[tiab] OR "Aspon-chlordane"[tiab] OR "BRN 1915474"[tiab] OR "Caswell No. 174"[tiab] OR "CCRIS 127"[tiab] OR "Clordan"[tiab] OR "Clordano"[tiab] OR "Dichlorochlordene"[tiab] OR "EINECS 200-349-0"[tiab] OR "ENT 25,552-X"[tiab] OR "ENT 9,932"[tiab] OR "EPA Pesticide Chemical Code 058201"[tiab] OR "Ginsenoside compound K"[tiab] OR "HSDB 802"[tiab] OR "Intox 8"[tiab] OR "Kilex lindane"[tiab] OR "NCI-C00099"[tiab] OR "Octa-klor"[tiab] OR "Octachlorodihydrodicyclopentadiene"[tiab] OR "OMS 1437"[tiab] OR "RCRA waste number U036"[tiab] OR "SD 5532"[tiab] OR "Shell SD-5532"[tiab] OR "Synklor"[tiab] OR "Termi-ded"[tiab] OR "Topichlor 20"[tiab] OR "Topiclor"[tiab] OR "Topiclor 20"[tiab] OR "UN 2996"[tiab] OR "UNII-A9RLM212CY"[tiab] OR "Velsicol 1068"[tiab])

C.3.9 Monochlorobenzene (Chlorobenzene) (CAS# 108-90-7 | DTXSID4020298)

A standard literature search was conducted for monochlorobenzene using the search parameters shown in Table C-14 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-14. Set #1 of Search Strategy for Monochlorobenzene

Chemical	Monochlorobenzene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/01/22
Synonyms	("108-90-7"[rn] OR "108-90-7"[tiab] OR "Benzene, chloro-"[tiab] OR "Chlorobenzene"[tiab] OR "Monochlorobenzene"[tiab] OR "Benzene chloride"[tiab] OR "Chlorbenzol"[tiab] OR "Chlorobenzol"[tiab] OR "IP Carrier T 40"[tiab] OR "NSC 8433"[tiab] OR "Phenyl chloride"[tiab] OR "Tetrosin SP"[tiab] OR "DTXSID4020298"[tiab] OR "AI3-07776"[tiab] OR "Caswell No. 183A"[tiab] OR "CCRIS 1357"[tiab] OR "Chlorbenzene"[tiab] OR "Chlorobenzene, mono-"[tiab] OR "CP 27"[tiab] OR "EC 203-628-5"[tiab] OR "EINECS 203-628-5"[tiab] OR "EPA Pesticide Chemical Code 056504"[tiab] OR "HSDB 55"[tiab] OR "I P Carrier T 40"[tiab] OR "Monochlorbenzene"[tiab] OR "NCI-C54886"[tiab] OR "UNII-K18102WN1G"[tiab])

C.3.10 Cyanide (CAS# 57-12-5 | DTXSID6023991)

A standard literature search was conducted for cyanide using the search parameters shown in Table C-15 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-15. Set #1 of Search Strategy for Cyanide

Chemical	Cyanide
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	01/25/22
Synonyms	("57-12-5"[rn] OR "Cyanide"[tiab] OR "Cyanide, free"[tiab] OR "Hydrocyanato, ion(1-)"[tiab] OR "Carbon nitride ion (CN1-)"[tiab] OR "Cyanide(1-)"[tiab] OR "Cyanide(1-) ion"[tiab] OR "Cyanide anion"[tiab] OR "Cyanide (CN1-)"[tiab] OR "Cyanide ion"[tiab] OR "Cyanide ion(1-)"[tiab] OR "Cyanide ion (CN(1-))"[tiab] OR "Cyanides"[tiab] OR "Hydrocyanic acid, ion(1-)"[tiab] OR "Isocyanide"[tiab] OR "Nitrile anion"[tiab] OR "UN 1588"[tiab] OR "UN 1935"[tiab] OR "DTXSID6023991"[tiab] OR "BRN 1900509"[tiab] OR "Carbon nitride ion (CN(sup 1-))"[tiab] OR "Cyanide (CN(sup 1-))"[tiab] OR "Cyanide ions"[tiab] OR "Hydrocyanic acid, ion(1-)-"[tiab] OR "RCRA waste number P030"[tiab] OR "UNII-OXN4E7L11K"[tiab] OR "cyanides"[mh] OR "57-12-5"[tiab])

C.3.11 1,2-Dibromo-3-chloropropane (DBCP) (CAS# 96-12-8 | DTXSID3020413)

A standard literature search was conducted for 1,2-dibromo-3-chloropropane using the search parameters shown in Table C-16 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-16. Set #1 of Search Strategy for 1,2-Dibromo-3-chloropropane

Chemical	1,2-Dibromo-3-chloropropane
Assessment for Date Limit	CalEPA (2020, 10534721)
Search Date Limit	12/01/16
Search Date	03/07/22
Synonyms	("DTXSID3020413"[tiab] OR "96-12-8"[rn] OR "96-12-8"[tiab] OR "1,2-Dibromo-3-chloropropane"[tiab] OR "DBCP"[tiab] OR "Nemagon 20"[tiab] OR "OS 1897"[tiab] OR "Propane, 1,2-dibromo-3-chloro-"[tiab] OR "1-Chloro-2,3-dibromopropane"[tiab] OR "3-Chloro-1,2-dibromopropane"[tiab] OR "Dibromochloropropane"[tiab] OR "Fumazone"[tiab] OR "Nemafume"[tiab] OR "Nemagon"[tiab] OR "Nemagon 20G"[tiab] OR "Nemagon Soil Fumigant"[tiab] OR "Nemapaz"[tiab] OR "Nemazon"[tiab] OR "NSC 1512"[tiab] OR "UN 2872"[tiab] OR "1,2-Dibromochloropropane"[tiab] OR "2,3-Dibromo-1-chloropropane"[tiab] OR "3-01-00-00250 (Beilstein Handbook Reference)"[tiab] OR "AI3-18445"[tiab] OR "BBC 12"[tiab] OR "BBCP"[tiab] OR "BRN 1732077"[tiab] OR "Caswell No. 287"[tiab] OR "CCRIS 215"[tiab] OR "Durham Nematicode EM 17.1"[tiab] OR "EC 202-479-3"[tiab] OR "EINECS 202-479-3"[tiab] OR "EPA Pesticide Chemical Code 011301"[tiab] OR "Fumagon"[tiab] OR "Fumazon 86"[tiab] OR "Fumazone 86"[tiab] OR "Fumazone 86E"[tiab] OR "Gro-Tone Nematode Granular"[tiab] OR "HSDB 1629"[tiab] OR "NCI-C00500"[tiab] OR "Nemabrom"[tiab] OR "Nemagon 206"[tiab] OR "Nemagon 90"[tiab] OR "Nemagone"[tiab] OR "Nemanax"[tiab] OR "Nemanex"[tiab] OR "Nemaset"[tiab] OR "Nematocide EM 12.1"[tiab] OR "Nematocide EM 15.1"[tiab] OR "Nematocide Solution EM 17.1"[tiab] OR "Nematox"[tiab] OR "Oxy DBCP"[tiab] OR "Propane, 1-chloro-2,3-dibromo-"[tiab] OR "RCRA waste number U066"[tiab] OR "SD 1897"[tiab] OR "UNII-96K0FD4803"[tiab])

C.3.12 1,1-Dichloroethylene (CAS# 75-35-4 | DTXSID8021438)

A standard literature search was conducted for 1,1-dichloroethylene using the search parameters shown in Table C-17 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-17. Set #1 of Search Strategy for 1,1-Dichloroethylene

Chemical	1,1-Dichloroethylene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/24/22
Synonyms	("1,1-Dichloroethene"[tiab] OR "1,1-Dichloroethylene"[tiab] OR "75-35-4"[rn] OR "75-35-4"[tiab] OR "Ethene, 1,1-dichloro-"[tiab] OR "Vinylidene chloride"[tiab] OR "1,1-DICHLORAETHEN"[tiab] OR "1,1-Dichlorethylen"[tiab] OR "Diofan A 565S"[tiab] OR "Ethene, 1,1-dichloro"[tiab] OR

Chemical	1,1-Dichloroethylene
	"Ethylene, 1,1-dichloro-"[tiab] OR "Iso-dichloroethylene"[tiab] OR "UN 1303"[tiab] OR "Vinylidene dichloride"[tiab] OR "DTXSID8021438"[tiab] OR "1,1-Dce"[tiab] OR "AI3-28804"[tiab] OR "as-Dichloroethylene"[tiab] OR "asym-Dichloroethylene"[tiab] OR "CCRIS 622"[tiab] OR "EC 200-864-0"[tiab] OR "EINECS 200-864-0"[tiab] OR "HSDB 1995"[tiab] OR "NCI-C54262"[tiab] OR "RCRA waste number U078"[tiab] OR "UNII-21SK105J9D"[tiab] OR "VDC"[tiab] OR "Vinylidene chloride (II)"[tiab] OR "Vinylidene chloride (inhibited)"[tiab] OR "Vinylidene chloride, monomer"[tiab] OR "Vinylidine chloride"[tiab])

C.3.13 cis-1,2-Dichloroethylene (CAS# 156-59-2 | DTXSID2024030)

A standard literature search was conducted for cis-1,2-dichloroethylene using the search parameters shown in Table C-18 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-18. Set #1 of Search Strategy for cis-1,2-Dichloroethylene

Chemical	cis-1,2-Dichloroethylene
Assessment for Date Limit	CalEPA (2018a, 10489860)
Search Date Limit	07/01/17
Search Date	03/23/22
Synonyms	("156-59-2"[rn] OR "156-59-2"[tiab] OR "cis-1,2-Dichloroethylene"[tiab] OR "Ethene, 1,2-dichloro-, (Z)-"[mh] OR "(Z)-1,2-Dichloroethene"[tiab] OR "(Z)-1,2-Dichloroethylene"[tiab] OR "1,2-cis-Dichloroethene"[tiab] OR "1,2-cis-Dichloroethylene"[tiab] OR "cis-1,2-Dichlorethylene"[tiab] OR "cis-1,2-Dichloroethene"[tiab] OR "cis-Dichlorethylen"[tiab] OR "cis-Dichloroethene"[tiab] OR "cis-Dichloroethylene"[tiab] OR "Ethene, 1,2-dichloro-, (1Z)-"[tiab] OR "Ethylene, 1,2-dichloro-, (Z)-"[tiab] OR "DTXSID2024030"[tiab] OR "4-01-00-00707 (Beilstein Handbook Reference)"[tiab] OR "Acetalyne dichloride"[tiab] OR "Acetylene dichloride, cis-"[tiab] OR "AI3-28863"[tiab] OR "BRN 1071208"[tiab] OR "CCRIS 4605"[tiab] OR "EINECS 205-859-7"[tiab] OR "HCC 1130c"[tiab] OR "HSDB 5656"[tiab] OR "NSC 6149"[tiab] OR "R 1130c"[tiab] OR "UNII-FYO9G15JYD"[tiab])

C.3.14 Dichloromethane (CAS# 75-09-2 | DTXSID0020868)

A standard literature search was conducted for dichloromethane using the search parameters shown in Table C-19 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-19. Set #1 of Search Strategy for Dichloromethane

Chemical	Dichloromethane
Assessment for Date Limit	EPA (2020i, 6811894)
Search Date Limit	03/01/16
Search Date	01/27/22
Synonyms	("75-09-2"[rn] OR "Dichloromethane"[tiab] OR "Methane, dichloro-"[tiab] OR "Methylene chloride"[tiab] OR "Aerothene MM"[tiab] OR "Cloruro de Metileno"[tiab] OR "Dichlormethan"[tiab] OR "Dichoromethane"[tiab] OR "diclorometano"[tiab] OR "Metaclen"[tiab] OR "Methane dichloride"[tiab] OR "METHYLENE DICHLORIDE"[tiab] OR "Narkotil"[tiab] OR "NSC 406122"[tiab] OR "Solaesthin"[tiab] OR "Soleana VDA"[tiab] OR "Solmethine"[tiab] OR "UN

Chemical	Dichloromethane
	1593"[tiab] OR "UN 1912"[tiab] OR "DTXSID0020868"[tiab] OR "4-01-00-00035 (Beilstein Handbook Reference)"[tiab] OR "AI3-01773"[tiab] OR "BRN 1730800"[tiab] OR "Caswell No. 568"[tiab] OR "CCRIS 392"[tiab] OR "EC 200-838-9"[tiab] OR "EINECS 200-838-9"[tiab] OR "EPA Pesticide Chemical Code 042004"[tiab] OR "F 30 (chlorocarbon)"[tiab] OR "Freon 30"[tiab] OR "HCC 30"[tiab] OR "HSDB 66"[tiab] OR "Khladon 30"[tiab] OR "Methylene bichloride"[tiab] OR "Methylenum chloratum"[tiab] OR "NCI-C50102"[tiab] OR "R30 (refrigerant)"[tiab] OR "RCRA waste number U080"[tiab] OR "UNII-588X2YUY0A"[tiab] OR "75-09-2"[tiab] OR "Methylene chloride"[mh])

C.3.15 1,2-Dichloropropane (CAS# 78-87-5 | DTXSID0020448)

A standard literature search was conducted for 1,2-dichloropropane using the search parameters shown in Table C-20 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-20. Set #1 of Search Strategy for 1,2-Dichloropropane

Chemical	1,2-Dichloropropane
Assessment for Date Limit	EPA (2020p, 10565936)
Search Date Limit	09/01/18
Search Date	09/28/22
Synonyms	("1,2-Dichloropropane"[tiab] OR "78-87-5"[rn] OR "78-87-5"[tiab] OR "Propane, 1,2-dichloro-"[tiab] OR "Propylene chloride"[tiab] OR "propylene dichloride"[tiab] OR "DTXSID0020448"[tiab] OR "3-01-00-00225 (Beilstein Handbook Reference)"[tiab] OR "AI3-15406"[tiab] OR "alpha,beta-Dichloropropane"[tiab] OR "alpha,beta-Propylene dichloride"[tiab] OR "BRN 1718880"[tiab] OR "Caswell No. 324"[tiab] OR "CCRIS 951"[tiab] OR "Dichloro-1,2 propane"[tiab] OR "EC 201-152-2"[tiab] OR "EINECS 201-152-2"[tiab] OR "ENT 15,406"[tiab] OR "EPA Pesticide Chemical Code 029002"[tiab] OR "HSDB 1102"[tiab] OR "NCI-C55141"[tiab] OR "NSC 1237"[tiab] OR "RCRA waste number U083"[tiab] OR "UNII-RRZ023OFWL"[tiab])

C.3.16 Di(2-ethylhexyl)adipate (CAS# 103-23-1 | DTXSID0020606)

A standard literature search was conducted for di(2-ethylhexyl)adipate using the search parameters shown in Table C-21 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-21. Set #1 of Search Strategy for Di(2-ethylhexyl)adipate

Chemical	Di(2-ethylhexyl)adipate
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/25/22
Synonyms	("103-23-1"[rn] OR "103-23-1"[tiab] OR "Adimoll DO"[tiab] OR "Adipic acid, bis(2-ethylhexyl) ester"[tiab] OR "Bis(2-ethylhexyl)hexanedioate"[tiab] OR "Bis(2-ethylhexyl) hexanedioate"[tiab] OR "DEHA"[tiab] OR "Hexanedioic acid, bis(2-ethylhexyl) ester"[tiab] OR "ADIPATE, BIS-2-ETHYLHEXYL"[tiab] OR "Adipate de bis(2-ethylhexyle)"[tiab] OR "ADIPATE, DI (2-ETHYLHEXYL)"[tiab] OR "ADIPATE, DI-(2-ETHYLHEXYL)"[tiab] OR "ADIPINSAEURE-BIS-(2-AETHYLHEXYL)-ESTER"[tiab] OR "Arlamol DOA"[tiab] OR "Bis(2-ethylhexyl)adipat"[tiab] OR "bis(2-ethylhexyl) adipate"[tiab] OR "BIS(2-ETHYLHEXYL)ADIPATE"[tiab] OR "Bisoflex

Chemical	Di(2-ethylhexyl)adipate
	DOA"[tiab] OR "Crodamol DOA"[tiab] OR "Dermol DOA"[tiab] OR "Diacizer DOA"[tiab] OR "Diethylhexyl adipate"[tiab] OR "Effomoll DA"[tiab] OR "Effomoll DOA"[tiab] OR "Ergoplast AdDO"[tiab] OR "Flexol A 26"[tiab] OR "Hatcol 2908"[tiab] OR "Hexanedioic acid, 1,6-bis(2-ethylhexyl) ester"[tiab] OR "Hexanedioic acid, bis(2-ethylhexyl)ester"[tiab] OR "Hexanoic acid bis(2-ethylhexyl) ester"[tiab] OR "Jayflex DOA 2"[tiab] OR "Kodaflex DOA"[tiab] OR "Lankroflex DOA"[tiab] OR "Monoplex DOA"[tiab] OR "NSC 56775"[tiab] OR "Octyl adipate"[tiab] OR "Plasthall DOA"[tiab] OR "Plastomoll DOA"[tiab] OR "Reomol DOA"[tiab] OR "Sansocizer DOA"[tiab] OR "Truflex DOA"[tiab] OR "Vestinol OA"[tiab] OR "Vistone A 10"[tiab] OR "Wickenol 158"[tiab] OR "Witamol 320"[tiab] OR "DTXSID0020606"[tiab] OR "Di-(2-ethylhexyl) adipate"[tiab] OR "Dioctyl adipate"[tiab] OR "4-02-00-01964 (Beilstein Handbook Reference)"[tiab] OR "Adipol 2EH"[tiab] OR "ADO (lubricating oil)"[tiab] OR "AI3-28579"[tiab] OR "BEHA"[tiab] OR "BRN 1803774"[tiab] OR "CCRIS 236"[tiab] OR "Di(2-ethylhexyl) adipate"[tiab] OR "Di(2-ethylhexyl)adipate"[tiab] OR "Di-2-ethylhexyl adipate"[tiab] OR "Dioctyl adipate (VAN)"[tiab] OR "EC 203-090-1"[tiab] OR "EINECS 203-090-1"[tiab] OR "Flexol plasticizer 10-A"[tiab] OR "Flexol plasticizer A-26"[tiab] OR "Hexanedioic acid, dioctyl ester"[tiab] OR "HSDB 343"[tiab] OR "K 3220"[tiab] OR "Kemester 5652"[tiab] OR "Mollan S"[tiab] OR "Morflex 310"[tiab] OR "NCI-C54386"[tiab] OR "Octyl adipate (VAN)"[tiab] OR "PX-238"[tiab] OR "Rucoflex Plasticizer DOA"[tiab] OR "Sicol 250"[tiab] OR "Staflex DOA"[tiab] OR "Uniflex DOA"[tiab] OR "UNII-MBY1SL921L"[tiab] OR "USS 700"[tiab])

C.3.17 Dinoseb (CAS# 88-85-7 | DTXSID3020207)

A standard literature search was conducted for dinoseb using the search parameters shown in Table C-22 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-22. Set #1 of Search Strategy for Dinoseb

Chemical	Dinoseb
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/07/22
Synonyms	("2-(Butan-2-yl)-4,6-dinitrophenol"[tiab] OR "2-sec-Butyl-4,6-dinitrophenol"[tiab] OR "88-85-7"[rn] OR "88-85-7"[tiab] OR "Dinoseb"[tiab] OR "Dinoseb acid"[tiab] OR "Phenol, 2-(1-methylpropyl)-4,6-dinitro-"[tiab] OR "2-(1-Methylpropyl)-4,6-dinitrophenol"[tiab] OR "2,4-Dinitro-6-(1-methylpropyl)phenol"[tiab] OR "2,4-Dinitro-6-sec-butylphenol"[tiab] OR "4,6-Dinitro-2-(1-methyl-n-propyl)phenol"[tiab] OR "4,6-Dinitro-2-(2-butyl)phenol"[tiab] OR "4,6-Dinitro-2-sec-butylphenol"[tiab] OR "4,6-Dinitro-o-sec-butylphenol"[tiab] OR "6-sec-Butyl-2,4-dinitrophenol"[tiab] OR "Blaartox"[tiab] OR "Butaphen"[tiab] OR "Butaphene"[tiab] OR "Chemox P.E."[tiab] OR "Desicoil"[tiab] OR "Dibutox"[tiab] OR "Dibutox 20CE"[tiab] OR "Dow General"[tiab] OR "Hivertox"[tiab] OR "Liro DNBP"[tiab] OR "NSC 202753"[tiab] OR "Phenol, 2-sec-butyl-4,6-dinitro-"[tiab] OR "Premerge"[tiab] OR "Super Kabrol"[tiab] OR "UN 2779"[tiab] OR "UN 2780"[tiab] OR "UN 3013"[tiab] OR "DTXSID3020207"[tiab] OR "4,6-Dinitro-2-(1-methyl-propyl)phenol"[tiab] OR "4,6-Dinitro-2-sec.butylfenol"[tiab] OR "4-06-00-03279 (Beilstein Handbook Reference)"[tiab] OR "Aatox"[tiab] OR "AI3-01122"[tiab] OR "Basanite"[tiab] OR "BNP 20"[tiab] OR "BNP 30"[tiab] OR "BRN 3211812"[tiab] OR "Caldon"[tiab] OR "Caswell No. 392DD"[tiab] OR "Chemox general"[tiab] OR "Chemox PE"[tiab] OR "DBNF"[tiab] OR "Dinitrall"[tiab] OR "Dinitro-ortho-sec-butyl phenol"[tiab] OR "Dinitrobutylphenol"[tiab] OR "DN 289"[tiab] OR "DNBP"[tiab] OR "DNOSBP"[tiab] OR "DNSBP"[tiab] OR "Dow General Weed Killer"[tiab] OR "Dow Selective Weed Killer"[tiab] OR "Dytop"[tiab] OR "EC 201-861-7"[tiab] OR "EINECS 201-861-7"[tiab] OR "Elgetol 318"[tiab] OR "ENT 1,122"[tiab] OR "EPA Pesticide Chemical Code 037505"[tiab] OR "Gebutox"[tiab] OR "Gebutox; knox-weed"[tiab] OR "Hel-Fire"[tiab] OR "HSDB 1445"[tiab] OR "Kiloseb"[tiab] OR "Knox-weed"[tiab] OR "Ladob"[tiab] OR

Chemical	Dinoseb
	"Laseb"[tiab] OR "Nitropone C"[tiab] OR "Phenotan"[tiab] OR "RCRA waste number P020"[tiab] OR "Sparic"[tiab] OR "Spurge"[tiab] OR "Subitex"[tiab] OR "Unicrop DNBP"[tiab] OR "UNII-YD44ZEM22M"[tiab] OR "Vertac Dinitro Weed Killer"[tiab] OR "Vertac General Weed Killer"[tiab] OR "Vertac Selective Weed Killer"[tiab] OR "WSX 8365"[tiab])

C.3.18 Dioxin (2,3,7,8-TCDD) (CAS# 1746-01-6 | DTXSID2021315)

A standard literature search was conducted for dioxin using the search parameters shown in Table C-23 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-23. Set #1 of Search Strategy for Dioxin

Chemical	Dioxin
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/08/22
Synonyms	("DTXSID2021315"[tiab] OR "1746-01-6"[rn] OR "1746-01-6"[tiab] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tiab] OR "2,3,7,8-Tetrachlorooxanthrene"[tiab] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tiab] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tiab] OR "Dioxin"[tiab] OR "Dioxin (herbicide contaminant)"[tiab] OR "UN 2811"[tiab] OR "2,3,7,8-TCDD"[tiab] OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin"[tiab] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tiab] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tiab] OR "2,3,7,8-tetrachlorodibenzo[b,e][1,4]dioxin"[tiab] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tiab] OR "2,3,7,8-Tetrachloro-p-dioxin"[tiab] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tiab] OR "p-Dioxin"[tiab] OR "Tetrachlorodibenzodioxin"[tiab] OR "Polychlorinated Dibenzodioxins"[mh] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tiab] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tiab] OR "5-19-02-00041 (Beilstein Handbook Reference)"[tiab] OR "BRN 0271116"[tiab] OR "CCRIS 576"[tiab] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tiab] OR "Dioxine"[tiab] OR "EINECS 217-122-7"[tiab] OR "HSDB 4151"[tiab] OR "NCI-C03714"[tiab] OR "TCDBD"[tiab] OR "TCDD"[tiab] OR "Tetrachlorodibenzo-p-dioxin"[tiab] OR "Tetradioxin"[tiab] OR "UNII-DO80M48B6O"[tiab])

C.3.19 Endrin (CAS# 72-20-8 | DTXSID6020561)

A standard literature search was conducted for endrin using the search parameters shown in Table C-24 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-24. Set #1 of Search Strategy for Endrin

Chemical	Endrin
Assessment for Date Limit	CalEPA (2016b, 10489859)
Search Date Limit	09/01/15
Search Date	08/14/23
Synonyms	("72-20-8" OR "Endrin" OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-" OR "rel-(1aR,2R,2aR,3R,6S,6aS,7S,7aS)-3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphtho[2,3-b]oxirene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-endo-1,4:5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo,

Chemical	Endrin
	endo-1,4:5,8-dimethanonaphthalene" OR "1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-, endo,endo-" OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aR,2R,2aR,3R,6S,6aS,7S,7aS)-rel-" OR "2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-" OR "Endricol" OR "endrine" OR "Experimental Insecticide 269" OR "Mendrin" OR "Oktanex" OR "Stardrin" OR "Stardrin 20" OR "DTXSID6020561" OR "(1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha)-3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene" OR "(1R,4S,4aS,5S,6S,7R,8R,8aR)-1,2,3,4,10,10-Hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-1R,4S,4aS,5S,6,7R,8R,8aR-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene" OR "1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo,endo-1,4:5,8-dimethanonaphthalene" OR "3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene" OR "3,4,5,6,9,9-Hexachloro-1aalpha,2beta,2abeta,3alpha,6alpha,6abeta,7beta,7aalpha-octahydro-2,7:3,6-dimethanonaphth(2,3-b)oxirene" OR "4-17-00-00525 (Beilstein Handbook Reference)" OR "AI3-17251" OR "BRN 0091397" OR "Caswell No. 423" OR "CCRIS 276" OR "Compound 269" OR "EINECS 200-775-7" OR "EN 57" OR "Endrex" OR "Endrin 20 EC" OR "Endrin isomer" OR "ENT 17,251" OR "EPA Pesticide Chemical Code 041601" OR "Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene" OR "Hexadrin" OR "HSDB 198" OR "NCI-C00157" OR "Nendrin" OR "NSC 8935" OR "OMS 197" OR "RCRA waste number P051" OR "SD 3419" OR "UNII-OB9NVE7YCL")

C.3.20 Epichlorohydrin (CAS# 106-89-8 | DTXSID1020566)

A standard literature search was conducted for epichlorohydrin using the search parameters shown in Table C-25 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-25. Set #1 of Search Strategy for Epichlorohydrin

Chemical	Epichlorohydrin
Assessment for Date Limit	EPA (2006c, 1260313)
Search Date Limit	10/01/01
Search Date	09/08/22
Synonyms	("106-89-8"[rn] OR "106-89-8"[tiab] OR "2-(Chloromethyl)oxirane"[tiab] OR "Epichlorhydrin"[mh] OR "Epichlorhydrin"[tiab] OR "Epichlorohydrin"[tiab] OR "Oxirane, 2-(chloromethyl)-"[tiab] OR "1,2-Epoxy-3-chloropropane"[tiab] OR "1-Chlor-2,3-epoxypropan"[tiab] OR "1-CHLOR-2,3-EPOXY-PROPAN"[tiab] OR "1-Chloro-2,3-epoxypropane"[tiab] OR "2,3-Epoxypropyl chloride"[tiab] OR "2-Chloropropylene oxide"[tiab] OR "3-Chloro-1,2-epoxypropane"[tiab] OR "3-Chloro-1,2-propylene oxide"[tiab] OR "3-Chloropropene-1,2-oxide"[tiab] OR "3-Chloropropylene oxide"[tiab] OR "(Chloromethyl)ethylene oxide"[tiab] OR "(Chloromethyl)oxirane"[tiab] OR "Chloropropylene oxide"[tiab] OR "COPOLYMER OF OXIRANE, (CHLOROMETHYL)-"[tiab] OR "dl-α-Epichlorohydrin"[tiab] OR "(. + -.)-Epichlorohydrin"[tiab] OR "Glycerol epichlorohydrin"[tiab] OR "Glycidyl chloride"[tiab] OR "NSC 6747"[tiab] OR "Oxirane, (chloromethyl)-"[tiab] OR "PROPANE, 1-CHLORO-2,3-EPOXY-"[tiab] OR "(RS)-Epichlorhydrin"[tiab] OR "UN 2023"[tiab] OR "α-Epichlorohydrin"[tiab] OR "γ-Chloropropylene oxide"[tiab] OR "DTXSID1020566"[tiab] OR "5-17-01-00020 (Beilstein Handbook Reference)"[tiab] OR "AI3-03545"[tiab] OR "alpha-Epichlorohydrin"[tiab] OR "BRN 0079785"[tiab] OR "Caswell No. 424"[tiab] OR "CCRIS 277"[tiab] OR "Chloromethyloxirane"[tiab] OR "EC 203-439-8"[tiab] OR "EINECS 203-439-8"[tiab] OR "EPA Pesticide Chemical Code 097201"[tiab] OR "epi-Chlorohydrin"[tiab] OR "Epichlorophydrin"[tiab] OR "Glycerol epichlorhydrin"[tiab] OR "HSDB 39"[tiab] OR "NCI-C07001"[tiab] OR "Oxirane, 2-(chloromethyl)"[tiab] OR "RCRA waste number U041"[tiab] OR "UNII-08OOR508C0"[tiab])

C.3.21 Fluoride (CAS# 16984-48-8 | DTXSID9049617)

Two literature searches were conducted for fluoride. One search was the standard literature search, with the addition of dental toxicology related terms, using search parameters shown in Table C-26 and Table C-27 and toxicology filters for PubMed® and Web of Science shown in Table C-26 and Table C-27, respectively.

Table C-26. Set #1 and Set #2 of Search Strategy for Fluoride in PubMed

Chemical	Fluoride
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/10/22
Set #1 (Synonyms)	("16984-48-8"[RN] OR "Fluoride"[TIAB] OR "Fluorides (as F)"[TIAB] OR "Hydrofluoric acid, ion(1-)"[TIAB] OR "Fluoride(1-)"[TIAB] OR "Fluoride ion"[TIAB] OR "Fluoride ion(1-)"[TIAB] OR "Fluoride ion (F-)"[TIAB] OR "Fluorides/fluorine/hydrogen fluoride"[TIAB] OR "Fluorine, ion"[TIAB] OR "Fluorine ion(1-)"[TIAB] OR "Fluorine ion(F1-)"[TIAB] OR "DTXSID9049617"[TIAB] OR "Fluorides"[TIAB] OR "Drinking water, fluoride treated"[TIAB] OR "Fluoride ion(F-)"[TIAB] OR "Fluorine ion"[TIAB] OR "UNII-Q80VPU408O"[TIAB] OR "Fluorides"[Mesh] OR "16984-48-8"[TIAB] OR "hydrofluosilicic acid"[tiab] OR "Sodium silicofluoride"[tiab])
Set #2 (Filter)	AND ("Toxicol Sci"[TA] OR (drug-induced abnormalities OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Biological Factors/adverse effects[Mesh] OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR chemical burns OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR chemical terrorism OR Chemically-Induced Disorders OR Clin Toxicol Phila[TA] OR Colony Collapse OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Drug Interactions OR drug therapy/adverse effects[Mesh] OR Drug-Induced Dyskinesia OR Endocrine System Diseases/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Enzymes and Coenzymes/adverse effects[Mesh] OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR food and beverages/adverse effects[Mesh] OR Genetic Phenomena/drug effects[Mesh] OR hazardous substances OR hepatotox* OR Heterocyclic Compounds/adverse effects[Mesh] OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Inorganic Chemicals/adverse effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR Macromolecular Substances/adverse effects[Mesh] OR manufactured materials/adverse effects[Mesh] OR Material Safety Data Sheets OR mental disorders/chemically induced[Mesh] OR Musculoskeletal Diseases/chemically induced[Mesh] OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Otorhinolaryngologic Diseases/chemically induced[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR pesticides/toxicity[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR toxic plants OR poison* OR poisoning OR substance-induced psychoses OR radiation-induced abnormalities OR Radioactive Hazard Release OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Drug Therapeutic Index OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR

Chemical	Fluoride
	Toxicology[TA] OR toxif* OR toxig*) OR "Neurotoxicity" OR "Neurotoxicity Syndromes"[Mesh] OR "memory" OR "memory"[Mesh] OR "bone mineralization osteosarcoma" OR "bone mineral density" OR "Bone Density"[Mesh] OR "Bone Density" OR "Thyroid" OR "Thyroid Gland"[Mesh] OR "Iodide" OR "Fluoridation" OR "Fluoridation"[Mesh] OR "Fluorosis" OR "Fluorosis, Dental"[Mesh] OR "dental products" OR "ground water" OR "Groundwater"[Mesh] OR "Groundwater" OR "Carries" OR "joint diseases" OR "Joint Diseases"[Mesh] OR "IQ" OR "Intelligence Quotient" OR "Genetics" OR "Genetics"[Mesh] OR "Kidney" OR "Kidney"[Mesh] OR "Geology" OR "dental treatments" OR "Toothpaste" OR "Geochemistry" OR "salt fluoridation")
Limit: Language	AND (English[lang])

Table C-27. Set #1 and Set #2 of Search Strategy for Fluoride in WoS

Chemical	Fluoride
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/10/22
Set #1 (Synonyms)	("16984-48-8"[RN] OR "Fluoride"[TIAB] OR "Fluorides (as F)"[TIAB] OR "Hydrofluoric acid, ion(1-)"[TIAB] OR "Fluoride(1-)"[TIAB] OR "Fluoride ion"[TIAB] OR "Fluoride ion(1-)"[TIAB] OR "Fluoride ion (F-)"[TIAB] OR "Fluorides/fluorine/hydrogen fluoride"[TIAB] OR "Fluorine, ion"[TIAB] OR "Fluorine ion(1-)"[TIAB] OR "Fluorine ion(F1-)"[TIAB] OR "DTXSID9049617"[TIAB] OR "Fluorides"[TIAB] OR "Drinking water, fluoride treated"[TIAB] OR "Fluoride ion(F-)"[TIAB] OR "Fluorine ion"[TIAB] OR "UNII-Q80VPU408O"[TIAB] OR "Fluorides"[Mesh] OR "16984-48-8"[TIAB] OR "hydrofluosilicic acid"[tiab] OR “Sodium silicofluoride”[tiab])
Set #2 (Filter)	AND (((“adverse effects”) AND (“Biomedical Materials” OR “Dental Materials” OR “Chemical Uses” OR “Complex Mixtures” OR “drug therapy” OR “Environment Health” OR “Public Health” OR food OR beverages OR Hormones OR “Hormone Substitutes” OR “Hormone Antagonists” OR “Pharmaceutical Preparations”)) OR ((“chemically induced” OR “chemical induced”) AND (“Disorders of Environmental Origin” OR “Environmental Disorders” OR “Endocrine System Diseases” OR “Pregnancy Complications” OR “mental disorders” OR “Musculoskeletal Diseases” OR “Neoplasms” OR “Cancer” OR “Nervous System Diseases” OR “Nutritional Diseases” OR “Pathological Conditions” OR “Pathological Signs” OR “Pathological Symptoms” OR “Stomatognathic Diseases” OR “Connective Tissue Diseases” OR “Liver injury”)) OR ((“drug effects” OR “drug induced”) AND (“Genetic Phenomena” OR “Reproductive Physiological Phenomena” OR “Urinary Physiological Phenomena” OR “liver injury”)) OR “drug-induced abnormalities” OR “adverse drug reaction reporting systems” OR carcinogen* OR Carcinogenesis OR “chemical hazard release” OR “chemical terrorism” OR “Chemically-Induced Disorders” OR “chemical induced disorders” OR “Drug Interactions” OR “Drug Recalls” OR “Environmental Health” OR “environmental illness” OR “environmental monitoring” OR “environmental pollutants” OR “environmental pollution” OR “forensic toxicology” OR “hazardous substances” OR hepatotox* OR immunotox* OR “Metabolic Inactivation” OR “Material Safety Data Sheets” OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR “occupational diseases” OR Pesticides OR poison* OR poisoning OR “substance-induced psychoses” OR terata* OR terato* OR Teratogenesis OR “Toxic Actions” OR toxic OR “toxicity tests” OR Toxicokinetics OR “Toxicological Phenomena” OR toxicology OR toxif* OR toxig* OR "Neurotoxicity" OR "memory" OR "bone mineralization osteosarcoma" OR "bone mineral density" OR "Bone Density" OR "Thyroid" OR "Iodide" OR "Fluoridation" OR "Fluorosis" OR "dental products" OR "ground water" OR "Groundwater" OR "Carries" OR "joint diseases" OR "IQ" OR "Intelligence Quotient" OR "Genetics" OR "Kidney" OR "Geology" OR "dental treatments" OR "Toothpaste" OR "Geochemistry" OR "salt fluoridation")

The other search was a targeted literature search focused on dental toxicology, such as dental caries and fluorosis. The search date limits were based on the time between the EPA Six-Year Review Summary {U.S. EPA 2016c, 6557097} and the next most recent health assessments, HC GDWQ {HC, 2010a, 10528541) and EPA OW Dose-Response Analysis for Noncancer Effects (Tables C-28 and C-29), respectively.

Table C-28. Set #1 and Set #2 of Dental Toxicology Search Strategy for Fluoride in PubMed

Chemical	Fluoride
Assessment for Date Limit	EPA (2010d, 10493692); HC (2010a, 10528541); and EPA (2016c, 6557097)
Search Date Limit	01/01/2010
Search Date	12/31/2014
Set #1 (Synonyms)	("16984-48-8"[RN] OR "Fluoride"[TIAB] OR "Fluorides (as F)"[TIAB] OR "Hydrofluoric acid, ion(1-)"[TIAB] OR "Fluoride(1-)"[TIAB] OR "Fluoride ion"[TIAB] OR "Fluoride ion(1-)"[TIAB] OR "Fluoride ion (F-)"[TIAB] OR "Fluorides/fluorine/hydrogen fluoride"[TIAB] OR "Fluorine, ion"[TIAB] OR "Fluorine ion(1-)"[TIAB] OR "Fluorine ion(F1-)"[TIAB] OR "DTXSID9049617"[TIAB] OR "Fluorides"[TIAB] OR "Drinking water, fluoride treated"[TIAB] OR "Fluoride ion(F-)"[TIAB] OR "Fluorine ion"[TIAB] OR "UNII-Q80VPU408O"[TIAB] OR "Fluorides"[Mesh] OR "16984-48-8"[TIAB] OR "hydrofluosilicic acid"[tiab] OR “Sodium silicofluoride”[tiab])
Set #2 (Filter)	AND ("Dental caries"[Mesh] OR "Dental caries"[TIAB] OR "Dental Cavities"[TIAB] OR "Dental fluorosis"[TIAB] OR "Enamel demineralization"[TIAB] OR "Fluoride intake"[TIAB] OR "Fluorosis, Dental"[Mesh] OR "Occlusal caries"[TIAB] OR "Interproximal caries"[TIAB] OR "Tooth cavities"[TIAB] OR "Tooth decay"[TIAB] OR "Tooth demineralization"[TIAB] OR "BMC Oral Health"[TA] OR "Caries Research"[TA] OR "Journal of Dentistry"[TA] OR "Journal of Dental Research"[TA])
Limit: Language	AND (English[lang])

Table C-29. Set #1 and Set #2 of Dental Toxicology Search Strategy for Fluoride in WoS

Chemical	Fluoride
Assessment for Date Limit	EPA (2010d, 10493692); HC (2010a, 10528541); and EPA (2016c, 6557097)
Search Date Limit	01/01/2010
Search Date	12/31/2014
Set #1 (Synonyms)	("16984-48-8"[RN] OR "Fluoride"[TIAB] OR "Fluorides (as F)"[TIAB] OR "Hydrofluoric acid, ion(1-)"[TIAB] OR "Fluoride(1-)"[TIAB] OR "Fluoride ion"[TIAB] OR "Fluoride ion(1-)"[TIAB] OR "Fluoride ion (F-)"[TIAB] OR "Fluorides/fluorine/hydrogen fluoride"[TIAB] OR "Fluorine, ion"[TIAB] OR "Fluorine ion(1-)"[TIAB] OR "Fluorine ion(F1-)"[TIAB] OR "DTXSID9049617"[TIAB] OR "Fluorides"[TIAB] OR "Drinking water, fluoride treated"[TIAB] OR "Fluoride ion(F-)"[TIAB] OR "Fluorine ion"[TIAB] OR "UNII-Q80VPU408O"[TIAB] OR "Fluorides"[Mesh] OR "16984-48-8"[TIAB] OR "hydrofluosilicic acid"[tiab] OR “Sodium silicofluoride”[tiab])
Set #2 (Filter)	AND ("Dental caries" OR "Dental caries" OR "Dental Cavities" OR "Dental fluorosis" OR "Enamel demineralization" OR "Fluoride intake" OR "Fluorosis, Dental" OR "Occlusal caries" OR "Interproximal caries" OR "Tooth cavities" OR "Tooth decay" OR "Tooth demineralization")

C.3.22 Heptachlor (CAS# 76-44-8 | DTXSID3020679)

A standard literature search was conducted for heptachlor using the search parameters shown in Table C-30 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-30. Set #1 of Search Strategy for Heptachlor

Chemical	Heptachlor
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/08/22
Synonyms	("76-44-8"[rn] OR "76-44-8"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-1H-4,7-methanoindene"[tiab] OR "4,7-Methano-1H-indene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-"[tiab] OR "Heptachlor"[mh] OR "Heptachlor"[tiab] OR "1,4,5,6,7,10,10-Heptachloro-4,7,8,9-tetrahydro-4,7-methyleneindene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3α,4,7,7α-tetrahydro-4,7-endo-methanoindene"[tiab] OR "3,4,5,6,8,8a-Heptachlorodicyclopentadiene"[tiab] OR "3-Chlorochlordene"[tiab] OR "4,7-Methano-1H-indene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-,"[tiab] OR "4,7-Methanoindene, 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-"[tiab] OR "Aahepta"[tiab] OR "Agroceres"[tiab] OR "Arbinex 30TN"[tiab] OR "ENT 15, 152"[tiab] OR "Heptachlor [1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methano-1H-indene]"[tiab] OR "Heptachlorane"[tiab] OR "heptachlore"[tiab] OR "heptacloro"[tiab] OR "NSC 8930"[tiab] OR "Rhodiachlor"[tiab] OR "Velsicol 104"[tiab] OR "DTXSID3020679"[tiab] OR "1(3a),4,5,6,7,8,8-Heptachloro-3a(1),4,7,7a-tetrahydro-4,7-methanoindene"[tiab] OR "1,4,5,6,7,10,10-Heptachloro-4,7,8,9-tetrahydro-4,7-endomethyleneindene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-endomethanoindene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanol-1H-indene"[tiab] OR "1,4,5,6,7,8,8-Heptachlorotetrahydro-4,7-methanoindene"[tiab] OR "1,4,5,6,7,8,8a-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane"[tiab] OR "3,4,5,6,7,8,8a-Heptachlorodicyclopentadiene"[tiab] OR "AI3-15152"[tiab] OR "alpha-Dicyclopentadiene, 3,4,5,6,7,8,8A-heptachloro-"[tiab] OR "Basaklor"[tiab] OR "Caswell No. 474"[tiab] OR "CCRIS 324"[tiab] OR "Dicyclopentadiene, 3,4,5,6,7,8,8a-heptachloro-"[tiab] OR "E 3314"[tiab] OR "EINECS 200-962-3"[tiab] OR "ENT 15,152"[tiab] OR "EPA Pesticide Chemical Code 044801"[tiab] OR "Gold Crest H-60, Termide"[tiab] OR "GPKh"[tiab] OR "H-34"[tiab] OR "H-60"[tiab] OR "Hepta"[tiab] OR "Heptachlor (technical grade)"[tiab] OR "Heptachlorotetrahydro-4,7-methanoindene"[tiab] OR "Heptagran"[tiab] OR "Heptagranox"[tiab] OR "Heptamak"[tiab] OR "Heptamul"[tiab] OR "Heptasol"[tiab] OR "Heptox"[tiab] OR "HSDB 554"[tiab] OR "NCI-C00180"[tiab] OR "OMS 193"[tiab] OR "RCRA waste number P059"[tiab] OR "Soleptax"[tiab] OR "Technical heptachlor"[tiab] OR "Velsicol heptachlor"[tiab])

C.3.23 Heptachlor epoxide (CAS# 1024-57-3 | DTXSID1024126)

A standard literature search was conducted for heptachlor epoxide using the search parameters shown in Table C-31 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-31. Set #1 of Search Strategy for Heptachlor Epoxide

Chemical	Heptachlor Epoxide
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14

Chemical	Heptachlor Epoxide
Search Date	03/09/22
Synonyms	("1024-57-3"[rn] OR "1024-57-3"[tiab] OR "(1aS,1bR,5R,5aS,6R,6aS)-2,3,4,5,6,7,7-Heptachloro-1b,2,5,5a,6,6a-hexahydro-1aH-2,5-methanoindeno[1,2-b]oxirene"[tiab] OR "2,5-Methano-2H-indeno[1,2-b]oxirene, 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-, (1aS,1bR,5R,5aS,6R,6aS)-"[tiab] OR "Epoxyheptachlor"[tiab] OR "Heptachlor epoxide B"[tiab] OR "2,5-Methano-2H-indeno[1,2-b]oxirene, 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-, (1aR,1bS,2R,5S,5aR,6S,6aR)-rel-"[tiab] OR "2,5-Methano-2H-indeno[1,2-b]oxirene, 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-, (1aα,1bβ,2α,5α,5aβ,6β,6aα)-"[tiab] OR "4,7-Methanoindan, 1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-"[tiab] OR "(.+-.)-cis-Heptachlor epoxide"[tiab] OR "cis-Heptachlor epoxide"[tiab] OR "GPKh epoxide"[tiab] OR "Heptachlor cis-oxide"[tiab] OR "Heptachlorepoxid"[tiab] OR "Heptachlor exo-epoxide"[tiab] OR "Heptepoxide"[tiab] OR "Velsicol 53CS17"[tiab] OR "DTXSID1024126"[tiab] OR "Heptachlor epoxide"[mh] OR "Heptachlor epoxide"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-2,3-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene"[tiab] OR "1,4,5,6,7,8,8-Heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindan"[tiab] OR "2,3,4,5,6,7,7-Heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2H-indeno(1,2-b)oxirene"[tiab] OR "2,5-Methano-2H-oxireno(a)indene, 2,3,4,5,6,7,7-heptachlor-1a,1b,5,5a,6,6a-hexahydro-"[tiab] OR "2,5-Methano-2H-oxireno(a)indene, 2,3,4,5,6,7,7-heptachloro-1a,1b,5,5a,6,6a-hexahydro-"[tiab] OR "AI3-25584"[tiab] OR "CCRIS 9452"[tiab] OR "EINECS 213-831-0"[tiab] OR "ENT 25,584"[tiab] OR "HSDB 6182"[tiab] OR "UNII-055UWF6R6I"[tiab])

C.3.24 Hexachlorobenzene (CAS# 118-74-1 | DTXSID2020682)

A standard literature search was conducted for hexachlorobenzene using the search parameters shown in Table C-32 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-32. Set #1 of Search Strategy for Hexachlorobenzene

Chemical	Hexachlorobenzene
Assessment for Date Limit	ATSDR (2015d, 4322480)
Search Date Limit	12/01/14
Search Date	03/10/22
Synonyms	("118-74-1"[rn] OR "118-74-1"[tiab] OR "1,2,3,4,5,6-Hexachloro-benzene"[tiab] OR "Benzene, 1,2,3,4,5,6-hexachloro-"[tiab] OR "HCB"[tiab] OR "Hexachlorobenzene"[mh] OR "Hexachlorobenzene"[tiab] OR "Anticarie"[tiab] OR "Benzenehexachloride"[tiab] OR "Benzene, hexachloro-"[tiab] OR "Bunt-cure"[tiab] OR "Bunt-no-more"[tiab] OR "Co-op Hexa"[tiab] OR "Hexachlorbenzol"[tiab] OR "Julin's carbon chloride"[tiab] OR "No Bunt"[tiab] OR "No Bunt Liquid"[tiab] OR "NSC 9243"[tiab] OR "Pentachlorophenyl chloride"[tiab] OR "Perchlorobenzene"[tiab] OR "Sanocide"[tiab] OR "Sniecioto x"[tiab] OR "UN 2729"[tiab] OR "Zaprawa nasienna sneciotox"[tiab] OR "DTXSID2020682"[tiab] OR "4-05-00-00670 (Beilstein Handbook Reference)"[tiab] OR "AI 3.01719"[tiab] OR "Amatin"[tiab] OR "BRN 1912585"[tiab] OR "Caswell No. 477"[tiab] OR "CCRIS 325"[tiab] OR "CEKU C.B."[tiab] OR "EINECS 204-273-9"[tiab] OR "ENT-1719"[tiab] OR "EPA Pesticide Chemical Code 061001"[tiab] OR "Granox"[tiab] OR "Granox NM"[tiab] OR "Hexa C.B."[tiab] OR "Hexa CB"[tiab] OR "HSDB 1724"[tiab] OR "NO Bunt 40"[tiab] OR "NO Bunt 80"[tiab] OR "Phenyl perchloryl"[tiab] OR "RCRA waste number U127"[tiab] OR "Sanocid"[tiab] OR "Smut-Go"[tiab] OR "UNII-4Z87H0LKUY"[tiab] OR "Voronit C"[tiab])

C.3.25 Hexachlorocyclopentadiene (CAS# 77-47-4 | DTXSID2020688)

A standard literature search was conducted for hexachlorocyclopentadiene using the search parameters shown in Table C-33 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-33. Set #1 of Search Strategy for Hexachlorocyclopentadiene

Chemical	Hexachlorocyclopentadiene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/18/22
Synonyms	("1,2,3,4,5,5-Hexachlorocyclopenta-1,3-diene"[tiab] OR "1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-"[tiab] OR "77-47-4"[rn] OR "77-47-4"[tiab] OR "HCCPD 1,3-Cyclopentadiene, 1,2,3,4,5,5-hexachloro-"[tiab] OR "Hexachlorocyclopentadiene"[tiab] OR "1,2,3,4,5,5-Hexachloro-1,3-cyclopentadiene"[tiab] OR "1,2,3,4,5,5-Hexachlorocyclopentadiene"[tiab] OR "CYCLOPENTADIENE, HEXACHLORO-"[tiab] OR "Graphlox"[tiab] OR "Hexachlorcyclopentadien"[tiab] OR "Hexachloro-1,3-cyclopentadiene"[tiab] OR "hexaclorociclopentadieno"[tiab] OR "NSC 9235"[tiab] OR "Perchlorocyclopentadiene"[tiab] OR "UN 2646"[tiab] OR "DTXSID2020688"[tiab] OR "1,3-Cyclopentadiene, hexachloro-"[tiab] OR "4-05-00-00381 (Beilstein Handbook Reference)"[tiab] OR "AI3-15558"[tiab] OR "BRN 0976722"[tiab] OR "C 56"[tiab] OR "C-56"[tiab] OR "C56"[tiab] OR "Caswell No. 478"[tiab] OR "CCRIS 5919"[tiab] OR "EINECS 201-029-3"[tiab] OR "EPA Pesticide Chemical Code 027502"[tiab] OR "HCCPD"[tiab] OR "HRS 1655"[tiab] OR "HSDB 4011"[tiab] OR "NCI-C55607"[tiab] OR "Perchloro-1,3-cyclopentadiene"[tiab] OR "RCRA waste number U130"[tiab] OR "UNII-IP6ATU242I"[tiab])

C.3.26 Lindane (CAS# 58-89-9 | DTXSID2020686)

A standard literature search was conducted for lindane using the search parameters shown in Table C-34 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-34. Set #1 of Search Strategy for Lindane

Chemical	Lindane
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/23/22
Synonyms	("(1R,2S,3r,4R,5S,6r)-1,2,3,4,5,6-Hexachlorocyclohexane"[tiab] OR "58-89-9"[rn] OR "58-89-9"[tiab] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-, (1alpha,2alpha,3beta,4alpha,5alpha,6beta)-"[tiab] OR "gamma-1,2,3,4,5,6-Hexachlorocyclohexane"[tiab] OR "gamma-HCH"[tiab] OR "gamma-Hexachlorocyclohexane"[tiab] OR "Lindane"[tiab] OR "1,2,3,4,5,6-G-HEXACHLOROCYCLOHEXANE"[tiab] OR "(1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-Hexachlorocyclohexane"[tiab] OR "Aalindan"[tiab] OR "Aficide"[tiab] OR "Agrocide"[tiab] OR "Agrocide III"[tiab] OR "Agrocide WP"[tiab] OR "Ameisenmittel Merck"[tiab] OR "Aparasin"[tiab] OR "Aphtiria"[tiab] OR "Aplidal"[tiab] OR "Arbitex"[tiab] OR "Arcotal S"[tiab] OR "Ben-Hex"[tiab] OR "Benhexol"[tiab] OR "Bercema-Spritz-Lindan 50"[tiab] OR "Celanex"[tiab] OR "Chloresene"[tiab] OR "Codechine"[tiab] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-, (1α,2α,3β,4α,5α,6β)-"[tiab] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-, γ-"[tiab] OR "Devoran"[tiab] OR "Dol Granule"[tiab] OR "Drilltox-Spezial Aglukon"[tiab] OR "Entomoxan"[tiab] OR "Esoderm"[tiab] OR "Fenoform forte"[tiab] OR "Forst-Nexen"[tiab] OR "Gamacid"[tiab] OR "Gamacide"[tiab] OR "Gamacide 20"[tiab] OR "Gamma benzene hexachloride"[tiab] OR

Chemical	Lindane
	"Gammalin"[tiab] OR "Gammalin 20"[tiab] OR "Gammaterr"[tiab] OR "Gammexane"[tiab] OR "Gamoline"[tiab] OR "Geobilan"[tiab] OR "Heclotox"[tiab] OR "Hexachloran"[tiab] OR "Hexachlorane"[tiab] OR "Hexatin"[tiab] OR "Hexaverm"[tiab] OR "Hexicide"[tiab] OR "Hexyclan"[tiab] OR "Hilbeech"[tiab] OR "Hungaria L 7"[tiab] OR "Jacutin"[tiab] OR "Kanodane"[tiab] OR "Kokotine"[tiab] OR "Lasochron"[tiab] OR "Lendine"[tiab] OR "Lidenal"[tiab] OR "Lindafor"[tiab] OR "Lindane [cyclohexane, 1,2,3,4,5,6-hexachloro-(1α,2α,3β,4α,5α,6β)-]"[tiab] OR "Lindane (g-BHC or g-HCH)"[tiab] OR "Lindatox"[tiab] OR "Lindosep"[tiab] OR "Lorexane"[tiab] OR "Mglawik L"[tiab] OR "Mszycol"[tiab] OR "Neo-Scabicidol"[tiab] OR "Nexen FB"[tiab] OR "Nexit Stark"[tiab] OR "Nexol E"[tiab] OR "Nicochloran"[tiab] OR "Omnitox"[tiab] OR "Ovadziak"[tiab] OR "Owadziak"[tiab] OR "Pedraczak"[tiab] OR "Pflanzol"[tiab] OR "Prodactif"[tiab] OR "Quellada"[tiab] OR "Sang-gamma"[tiab] OR "Scabecid"[tiab] OR "Scabene"[tiab] OR "Spritzlindane"[tiab] OR "Spritz-Rapidin"[tiab] OR "Spruehpflanzol"[tiab] OR "Streunex"[tiab] OR "Verindal Ultra"[tiab] OR "γ-1,2,3,4,5,6-Hexachlorocyclohexane"[tiab] OR "γ-Benzene hexachloride"[tiab] OR "γ-Benzohexachloride"[tiab] OR "γ-HCH or γ-BHC"[tiab] OR "γ-HCH ou γ-BHC"[tiab] OR "γ-HCH γ-BHC"[tiab] OR "γ-Hexachloran"[tiab] OR "γ-Hexachlorane"[tiab] OR "γ-Hexachlorobenzene"[tiab] OR "γ-Hexachlorocyclohexane"[tiab] OR "γ-Lindane"[tiab] OR "DTXSID2020686"[tiab] OR "Hexachlorocyclohexane"[mh] OR "Hexachlorocyclohexane"[tiab] OR "1,2,3,4,5,6-Hexachlorocyclohexane, gamma-isomer"[tiab] OR "4-05-00-00058 (Beilstein Handbook Reference)"[tiab] OR "Agrocide 6G"[tiab] OR "Agrocide 7"[tiab] OR "Agronexit"[tiab] OR "AI3-07796"[tiab] OR "Ameisentod"[tiab] OR "BBH"[tiab] OR "Bentox 10"[tiab] OR "Benzene hexachloride (Ambiguous)"[tiab] OR "Benzene hexachloride-gamma isomer"[tiab] OR "Benzene-1,2,3,4,5,6-hexachloride (Ambiguous)"[tiab] OR "Bexol"[tiab] OR "BHC (insecticide)"[tiab] OR "BRN 1907337"[tiab] OR "Caswell No. 079"[tiab] OR "Caswell No. 527"[tiab] OR "CCRIS 329"[tiab] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma-"[tiab] OR "Cyclohexane, 1,2,3,4,5,6-hexachloro-, gamma-isomer"[tiab] OR "Detmol Extract"[tiab] OR "Detox 25"[tiab] OR "EINECS 200-401-2"[tiab] OR "ENT 7,796"[tiab] OR "EPA Pesticide Chemical Code 009001"[tiab] OR "Gallogama"[tiab] OR "Gamacarbatox"[tiab] OR "Gamaphex"[tiab] OR "Gamene"[tiab] OR "Gamiso"[tiab] OR "gamma-Benzenehexachloride"[tiab] OR "gamma-Benzohexachloride"[tiab] OR "gamma-Hexachlorcyclohexanum"[tiab] OR "gamma-Hexachlorobenzene"[tiab] OR "Gamma-mean 400"[tiab] OR "Geolin G 3"[tiab] OR "Gexane"[tiab] OR "Hexachlorocyclohexane, gamma-isomer"[tiab] OR "Hexcidum"[tiab] OR "HGI"[tiab] OR "Hortex"[tiab] OR "HSDB 646"[tiab] OR "Hungaria L7"[tiab] OR "Inexit"[tiab] OR "Kwell"[tiab] OR "Lacco HI lin"[tiab] OR "Latka 666"[tiab] OR "Lentox"[tiab] OR "Lindagam"[tiab] OR "Lindagrain"[tiab] OR "Lindagranox"[tiab] OR "Lindanum"[tiab] OR "Lindapoudre"[tiab] OR "Lindex"[tiab] OR "Lintox"[tiab] OR "Linvur"[tiab] OR "Milbol 49"[tiab] OR "NCI-C00204"[tiab] OR "Nexit"[tiab] OR "Nexit-stark"[tiab] OR "Nexol-E"[tiab] OR "Novigam"[tiab] OR "NSC 755895"[tiab] OR "PLK"[tiab] OR "RCRA waste number U129"[tiab] OR "Sang gamma"[tiab] OR "Silvanol"[tiab] OR "TAP 85"[tiab] OR "Tri-6"[tiab] OR "UNII-59NEE7PCAB"[tiab] OR "Viton"[tiab])

C.3.27 Methoxychlor (CAS# 72-43-5 | DTXSID9020827)

A standard literature search was conducted for methoxychlor using the search parameters shown in Table C-35 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-35. Set #1 of Search Strategy for Methoxychlor

Chemical	Methoxychlor
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/09/22

Chemical	Methoxychlor
Synonyms	("1,1,1-trichloro-2,2-bis(p-methoxyphenyl)ethane"[tiab] OR "1,1'-(2,2,2-Trichloroethane-1,1-diyl)bis(4-methoxybenzene)"[tiab] OR "1,1'-(2,2,2-trichloroethylidene)bis[4-methoxybenzene]"[tiab] OR "72-43-5"[rn] OR "72-43-5"[tiab] OR "Benceno, 1,1 '- (2,2,2-tricloroetilideno) bis [4-metoxi"[tiab] OR "Benzene, 1,1'-(2,2,2-trichloroethylidene)bis[4-methoxy-"[tiab] OR "Methoxychlor"[mh] OR "Methoxychlor"[tiab] OR "Methoxychlor [Benzene, 1,1'-(2,2,2-trichloroethylidene)bis[4-methoxy-]"[tiab] OR "methoxychlore"[tiab] OR "MXC"[tiab] OR "p,p'-Methoxychlor"[tiab] OR "UN 2761 (DOT)"[tiab] OR "UN 3077"[tiab] OR "1,1,1-Trichloro-2,2-bis(4-methoxyphenyl)ethane"[tiab] OR "1,1,1-Trichloro-2,2-di(4-methoxyphenyl)ethane"[tiab] OR "1,1-(2,2,2-Trichloroethylidene)bis(4-methoxybenzene)"[tiab] OR "1,1-Bis(p-methoxyphenyl)-2,2,2-trichloroethane"[tiab] OR "2,2,2-Trichloro-1,1-bis(4-methoxyphenyl)ethane"[tiab] OR "2,2-Bis(4-methoxyphenyl)-1,1,1-trichloroethane"[tiab] OR "2,2-Bis(p-methoxyphenyl)-1,1,1-trichloroethane"[tiab] OR "2,2-Di-p-anisyl-1,1,1-trichloroethane"[tiab] OR "4,4'-(2,2,2-Trichloroethylidene)dianisole"[tiab] OR "Dimethoxy-DDT"[tiab] OR "Di(p-methoxyphenyl)(trichloromethyl)methane"[tiab] OR "Ethane, 1,1,1-trichloro-2,2-bis(p-methoxyphenyl)-"[tiab] OR "Marlate"[tiab] OR "Mesox K"[tiab] OR "Methoxcide"[tiab] OR "Methoxy-DDT"[tiab] OR "Mezox K"[tiab] OR "NSC 8945"[tiab] OR "p,p'-Dimethoxydiphenyltrichloroethane"[tiab] OR "p,p'-DMDT"[tiab] OR "p,p'-Methoxychlor"[tiab] OR "DTXSID9020827"[tiab] OR "1,1'-(2,2,2-Trichloroethylidene)bis(4-methoxybenzene)"[tiab] OR "1,1,1-Trichlor-2,2-bis(4-methoxy-phenyl)-aethan"[tiab] OR "1,1,1-Trichloro-2,2-bis(p-anisyl)ethane"[tiab] OR "2,2-Bis(p-anisyl)-1,1,1-trichloroethane"[tiab] OR "2,2-Di-(p-methoxyphenyl)-1,1,1-trichloroethane"[tiab] OR "4,4-(2,2,2-Trichloroethylidene)dianisole"[tiab] OR "4-06-00-06691 (Beilstein Handbook Reference)"[tiab] OR "BRN 2057367"[tiab] OR "Caswell No. 550"[tiab] OR "CCRIS 380"[tiab] OR "Chemform"[tiab] OR "Dianisyl trichloroethane"[tiab] OR "Dianisyltrichlorethane"[tiab] OR "DMDT"[tiab] OR "EINECS 200-779-9"[tiab] OR "ENT 1,716"[tiab] OR "EPA Pesticide Chemical Code 034001"[tiab] OR "Ethane, 2,2-bis(p-anisyl)-1,1,1-trichloro-"[tiab] OR "Higalmetox"[tiab] OR "HSDB 1173"[tiab] OR "Maralate"[tiab] OR "Methoxychlor 2 EC"[tiab] OR "Methoxychlor, technical"[tiab] OR "Metox"[tiab] OR "Moxie"[tiab] OR "NCI-C00497"[tiab] OR "OMS 466"[tiab] OR "RCRA waste number U247"[tiab])

C.3.28 Nitrate (as N) (CAS# 14797-55-8 | DTXSID5024217)

A standard literature search was conducted for nitrate, with the addition of hematologic disease terms to capture blue baby syndrome and methemoglobinemia. The search parameters and toxicology filters for PubMed® and Web of Science shown in Table C-36 and Table C-37, respectively.

Table C-36. Set #1 and Set #2 of Search Strategy for Nitrate in PubMed

Chemical	Nitrate
Assessment for Date Limit	CalEPA (2018c, 10489861)
Search Date Limit	07/01/16
Search Date	03/01/22
Set #1 (Synonyms)	("14797-55-8"[rn] OR "Nitrate"[tiab] OR "Nitrate(1-)"[tiab] OR "Nitrate ion"[tiab] OR "Nitrate ion(1-)"[tiab] OR "Nitrate ion (NO3-)"[tiab] OR "Nitrate (NO3-)"[tiab] OR "Nitrates/nitrites"[tiab] OR "Nitric acid, ion(1-)"[tiab] OR "DTXSID5024217"[tiab] OR "Nitrates"[tiab] OR "UNII-T93E9Y2844"[tiab] OR "Nitrates"[mh] OR "14797-55-8"[tiab])
Set #2 (Filter)	AND (“Toxicol Sci”[TA] OR (drug-induced abnormalities OR occupational accidents OR adverse drug reaction reporting systems OR Drug-Induced Akathisia OR Amino Acids, Peptides, and Proteins/adverse effects[Mesh] OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Background Radiation OR biohazard release OR Biological Factors/adverse effects[Mesh] OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR chemical burns OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically

Chemical	Nitrate
	induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR Chemical and Drug Induced Liver Injury OR chemical hazard release OR chemical terrorism OR Chemically-Induced Disorders OR Climate Change OR Clin Toxicol Phila[TA] OR Colony Collapse OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Digestive System Diseases/chemically induced[Mesh] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Drug Interactions OR Drug Recalls OR drug therapy/adverse effects[Mesh] OR Drug-Induced Dyskinesia OR ecotox* OR Ecotoxicology OR Endocrine System Diseases/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Environmental Restoration and Remediation OR Enzymes and Coenzymes/adverse effects[Mesh] OR Extreme Environments OR Eye Diseases/chemically induced[Mesh] OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR Fetal Alcohol Spectrum Disorders OR food and beverages/adverse effects[Mesh] OR forensic toxicology OR Genetic Phenomena/drug effects[Mesh] OR Global Warming OR hazardous substances OR Hemic and Lymphatic Diseases/chemically induced[Mesh] OR hepatotox* OR Heterocyclic Compounds/adverse effects[Mesh] OR Hormones, Hormone Substitutes, and Hormone Antagonists/adverse effects[Mesh] OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Inorganic Chemicals/adverse effects[Mesh] OR Integumentary System Physiological Phenomena/drug effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR LC50 OR Lipids/adverse effects[Mesh] OR Macromolecular Substances/adverse effects[Mesh] OR Male Urogenital Diseases/chemically induced[Mesh] OR manufactured materials/adverse effects[Mesh] OR Material Safety Data Sheets OR mental disorders/chemically induced[Mesh] OR Musculoskeletal Diseases/chemically induced[Mesh] OR mutagen* OR mutagenesis OR nanostructures OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nuclear Power Plants OR Nucleic Acids, Nucleotides, and Nucleosides/adverse effects[Mesh] OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Ocular Physiological Phenomena/drug effects[Mesh] OR Organic Chemicals/adverse effects[Mesh] OR Otorhinolaryngologic Diseases/chemically induced[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR persian gulf syndrome OR pesticides/toxicity[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR Phytochemicals/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR toxic plants OR poison* OR poisoning OR Polycyclic Compounds/adverse effects[Mesh] OR substance-induced psychoses OR radiation injuries OR Radiation Monitoring OR radiation-induced abnormalities OR Radioactive Hazard Release OR Radioactive Pollutants OR radiotherapy/adverse effects[Mesh] OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR Respiratory Tract Diseases/chemically induced[Mesh] OR Safety-Based Drug Withdrawals OR Skin and Connective Tissue Diseases/chemically induced[Mesh] OR Stomatognathic Diseases/chemically induced[Mesh] OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Drug Therapeutic Index OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR Toxicology[TA] OR toxif* OR toxig* OR Toxin-Antitoxin Systems OR venoms/toxicity[Mesh]) OR “Hematologic Diseases” OR “Methemoglobinemia"[Mesh] OR "Methemoglobinemia" OR “Blue Baby Syndrome”)
Limit: Language	AND (English[lang])

Table C-37. Set #1 and Set #2 of Search Strategy for Nitrate in WoS

Chemical	Nitrate
Assessment for Date Limit	CalEPA (2018c, 10489861)
Search Date Limit	07/01/16
Search Date	03/01/22
Set #1 (Synonyms)	("14797-55-8"[rn] OR "Nitrate"[tiab] OR "Nitrate(1-)"[tiab] OR "Nitrate ion"[tiab] OR "Nitrate ion(1-)"[tiab] OR "Nitrate ion (NO3-)"[tiab] OR "Nitrate (NO3-)"[tiab] OR "Nitrates/nitrites"[tiab] OR "Nitric acid, ion(1-)"[tiab] OR "DTXSID5024217"[tiab] OR "Nitrates"[tiab] OR "UNII-T93E9Y2844"[tiab] OR "Nitrates"[mh] OR "14797-55-8"[tiab])
Set #2 (Filter)	AND ((“adverse effects” AND (“Amino Acids, Peptides, and Proteins “ OR “Biological Factors “ OR “Biomedical Materials” OR “Dental Materials” OR Carbohydrates OR “Chemical Actions” OR “Chemical Uses” OR “Complex Mixtures” OR “drug therapy” OR “Environment Health” OR “Public Health” OR Enzymes OR Coenzymes OR food OR beverages OR Hormones OR “Hormone Substitutes” OR “Hormone Antagonists” OR “Heterocyclic Compounds” OR “household products” OR Lipids OR “Macromolecular Substances” OR “Nucleic Acids” OR Nucleotides OR Nucleosides “Pharmaceutical Preparations” OR Phytochemicals OR “Polycyclic Compounds” OR radiotherapy)) OR ((“chemically induced” OR “chemical induced”) AND (“Animal Diseases” OR “Cardiovascular Diseases” OR “Congenital Diseases” OR “Congenital Abnormalities” OR “Hereditary Diseases” OR “Hereditary Abnormalities” OR “Neonatal Diseases” OR “Neonatal Abnormalities” OR “Digestive System Diseases” OR “Disorders of Environmental Origin” OR “Environmental Disorders” OR “Endocrine System Diseases” OR “Eye Diseases” OR “Urogenital Diseases” OR “Pregnancy Complications” OR “Hemic Diseases” OR “Lymphatic Diseases” OR “Immune System Diseases” OR “Immune Diseases” OR “mental disorders” OR “Musculoskeletal Diseases” OR “Neoplasms” OR “Cancer” OR “Nervous System Diseases” OR “Nutritional Diseases” OR “Metabolic Diseases” OR “Otorhinolaryngologic Diseases” OR “Pathological Conditions” OR “Pathological Signs” OR “Pathological Symptoms” OR “Respiratory Tract Diseases” OR “Stomatognathic Diseases” OR “Skin Diseases” OR “Connective Tissue Diseases” OR “Liver injury”)) OR ((“drug effects” OR “drug induced”) AND (“birth weight” OR “Genetic Phenomena” OR “Integumentary System Physiological Phenomena” OR “Ocular Physiological Phenomena” OR “Reproductive Physiological Phenomena” OR “Urinary Physiological Phenomena” OR “liver injury”)) OR “drug-induced abnormalities” OR “occupational accidents” OR “adverse drug reaction reporting systems” OR “Drug-Induced Akathisia” OR “biohazard release” OR “chemical burns” OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR “chemical hazard release” OR “chemical terrorism” OR “Chemically-Induced Disorders” OR “chemical induced disorders” OR “Colony Collapse” OR “Drug Interactions” OR “Drug Recalls” OR “Drug-Induced Dyskinesia” OR ecotox* OR Ecotoxicology OR “Environmental Health” OR “environmental illness” OR “environmental monitoring” OR “environmental pollutants” OR “environmental pollution” OR “Environmental Restoration” OR “Environmental Remediation” OR “Fetal Alcohol Spectrum” OR “forensic toxicology” OR “hazardous substances” OR hepatotox* OR immunotox* OR “Metabolic Inactivation” OR “LC50” OR “Material Safety Data Sheets” OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR “occupational diseases” OR “persian gulf syndrome” OR Pesticides OR poison* OR poisoning OR “substance-induced psychoses” OR terata* OR terato* OR Teratogenesis OR “Toxic Actions” OR toxic OR “toxicity tests” OR Toxicokinetics OR “Toxicological Phenomena” OR toxicology OR toxif* OR toxig* OR “Toxin-Antitoxin Systems” OR “Hematologic Diseases” OR “Methemoglobinemia” OR “Blue Baby Syndrome”)

C.3.29 Nitrite (as N) (CAS# 14797-65-0 | DTXSID5024219)

A standard literature search was conducted for nitrite, with the addition of hematologic disease terms to capture blue baby syndrome and methemoglobinemia. The search parameters and toxicology filters for PubMed® and Web of Science shown in Table C-38 and Table C-39, respectively.

Table C-38. Set #1 and Set #2 of Search Strategy for Nitrite in PubMed

Chemical	Nitrite
Assessment for Date Limit	CalEPA (2018c, 10489861)
Search Date Limit	07/01/16
Search Date	02/03/22
Set #1 (Synonyms)	("14797-65-0"[rn] OR "Nitrite"[tiab] OR "Nitrite(1-)"[tiab] OR "Nitrite anion"[tiab] OR "Nitrite ion"[tiab] OR "Nitrite ion(1-)"[tiab] OR "Nitrite ion (NO2-)"[tiab] OR "Nitrogen dioxide(1-)"[tiab] OR "Nitrogen dioxide ion(1-)"[tiab] OR "Nitrogen peroxide ion(1-)"[tiab] OR "Nitrous acid, ion(1-)"[tiab] OR "DTXSID5024219"[tiab] OR "Nitrogen protoxide"[tiab] OR "UNII-J39976L608"[tiab] OR "14797-65-0"[tiab] OR "Nitrites"[tiab] OR "Nitrites"[mh])
Set #2 (Filter)	AND ("Toxicol Sci"[TA] OR (drug-induced abnormalities OR occupational accidents OR adverse drug reaction reporting systems OR Drug-Induced Akathisia OR Amino Acids, Peptides, and Proteins/adverse effects[Mesh] OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Background Radiation OR biohazard release OR Biological Factors/adverse effects[Mesh] OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR chemical burns OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR Chemical and Drug Induced Liver Injury OR chemical hazard release OR chemical terrorism OR Chemically-Induced Disorders OR Climate Change OR Clin Toxicol Phila[TA] OR Colony Collapse OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Digestive System Diseases/chemically induced[Mesh] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Drug Interactions OR Drug Recalls OR drug therapy/adverse effects[Mesh] OR Drug-Induced Dyskinesia OR ecotox* OR Ecotoxicology OR Endocrine System Diseases/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Environmental Restoration and Remediation OR Enzymes and Coenzymes/adverse effects[Mesh] OR Extreme Environments OR Eye Diseases/chemically induced[Mesh] OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR Fetal Alcohol Spectrum Disorders OR food and beverages/adverse effects[Mesh] OR forensic toxicology OR Genetic Phenomena/drug effects[Mesh] OR Global Warming OR hazardous substances OR Hemic and Lymphatic Diseases/chemically induced[Mesh] OR hepatotox* OR Heterocyclic Compounds/adverse effects[Mesh] OR Hormones, Hormone Substitutes, and Hormone Antagonists/adverse effects[Mesh] OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Inorganic Chemicals/adverse effects[Mesh] OR Integumentary System Physiological Phenomena/drug effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR LC50 OR Lipids/adverse effects[Mesh] OR Macromolecular Substances/adverse effects[Mesh] OR Male Urogenital Diseases/chemically induced[Mesh] OR manufactured materials/adverse effects[Mesh] OR Material Safety Data Sheets OR mental disorders/chemically induced[Mesh] OR Musculoskeletal Diseases/chemically induced[Mesh] OR mutagen* OR mutagenesis OR nanostructures OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nuclear Power Plants OR Nucleic Acids, Nucleotides, and Nucleosides/adverse effects[Mesh] OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Ocular Physiological Phenomena/drug effects[Mesh] OR Organic Chemicals/adverse effects[Mesh] OR Otorhinolaryngologic Diseases/chemically induced[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR persian gulf syndrome OR pesticides/toxicity[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR Phytochemicals/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR toxic plants OR poison* OR poisoning OR Polycyclic Compounds/adverse effects[Mesh] OR substance-induced psychoses OR radiation injuries OR

Chemical	Nitrite
	Radiation Monitoring OR radiation-induced abnormalities OR Radioactive Hazard Release OR Radioactive Pollutants OR radiotherapy/adverse effects[Mesh] OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR Respiratory Tract Diseases/chemically induced[Mesh] OR Safety-Based Drug Withdrawals OR Skin and Connective Tissue Diseases/chemically induced[Mesh] OR Stomatognathic Diseases/chemically induced[Mesh] OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Drug Therapeutic Index OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR Toxicology[TA] OR toxif* OR toxig* OR Toxin-Antitoxin Systems OR venoms/toxicity[Mesh]) OR “Hematologic Diseases” OR “Methemoglobinemia"[Mesh] OR "Methemoglobinemia" OR “Blue Baby Syndrome”)
Limit: Language	AND (English[lang])

Table C-39. Set #1 and Set #2 of Search Strategy for Nitrite in WoS

Chemical	Nitrite
Assessment for Date Limit	CalEPA (2018c, 10489861)
Search Date Limit	07/01/16
Search Date	02/03/22
Set #1 (Synonyms)	("14797-65-0"[rn] OR "Nitrite"[tiab] OR "Nitrite(1-)"[tiab] OR "Nitrite anion"[tiab] OR "Nitrite ion"[tiab] OR "Nitrite ion(1-)"[tiab] OR "Nitrite ion (NO2-)"[tiab] OR "Nitrogen dioxide(1-)"[tiab] OR "Nitrogen dioxide ion(1-)"[tiab] OR "Nitrogen peroxide ion(1-)"[tiab] OR "Nitrous acid, ion(1-)"[tiab] OR "DTXSID5024219"[tiab] OR "Nitrogen protoxide"[tiab] OR "UNII-J39976L608"[tiab] OR "14797-65-0"[tiab] OR "Nitrites"[tiab] OR "Nitrites"[mh])
Set #2 (Filter)	AND ((“adverse effects” AND (“Amino Acids, Peptides, and Proteins “ OR “Biological Factors “ OR “Biomedical Materials” OR “Dental Materials” OR Carbohydrates OR “Chemical Actions” OR “Chemical Uses” OR “Complex Mixtures” OR “drug therapy” OR “Environment Health” OR “Public Health” OR Enzymes OR Coenzymes OR food OR beverages OR Hormones OR “Hormone Substitutes” OR “Hormone Antagonists” OR “Heterocyclic Compounds” OR “household products” OR Lipids OR “Macromolecular Substances” OR “Nucleic Acids” OR Nucleotides OR Nucleosides “Pharmaceutical Preparations” OR Phytochemicals OR “Polycyclic Compounds” OR radiotherapy)) OR ((“chemically induced” OR “chemical induced”) AND (“Animal Diseases” OR “Cardiovascular Diseases” OR “Congenital Diseases” OR “Congenital Abnormalities” OR “Hereditary Diseases” OR “Hereditary Abnormalities” OR “Neonatal Diseases” OR “Neonatal Abnormalities” OR “Digestive System Diseases” OR “Disorders of Environmental Origin” OR “Environmental Disorders” OR “Endocrine System Diseases” OR “Eye Diseases” OR “Urogenital Diseases” OR “Pregnancy Complications” OR “Hemic Diseases” OR “Lymphatic Diseases” OR “Immune System Diseases” OR “Immune Diseases” OR “mental disorders” OR “Musculoskeletal Diseases” OR “Neoplasms” OR “Cancer” OR “Nervous System Diseases” OR “Nutritional Diseases” OR “Metabolic Diseases” OR “Otorhinolaryngologic Diseases” OR “Pathological Conditions” OR “Pathological Signs” OR “Pathological Symptoms” OR “Respiratory Tract Diseases” OR “Stomatognathic Diseases” OR “Skin Diseases” OR “Connective Tissue Diseases” OR “Liver injury”)) OR ((“drug effects” OR “drug induced”) AND (“birth weight” OR “Genetic Phenomena” OR “Integumentary System Physiological Phenomena” OR “Ocular Physiological Phenomena” OR “Reproductive Physiological Phenomena” OR “Urinary Physiological Phenomena” OR “liver injury”)) OR “drug-induced abnormalities” OR “occupational accidents” OR “adverse drug reaction reporting systems” OR “Drug-Induced Akathisia” OR “biohazard release” OR “chemical burns” OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR “chemical hazard release” OR “chemical terrorism” OR “Chemically-Induced Disorders” OR “chemical induced disorders” OR “Colony Collapse” OR “Drug Interactions” OR “Drug Recalls” OR “Drug-Induced Dyskinesia” OR ecotox* OR Ecotoxicology OR “Environmental Health” OR “environmental illness” OR “environmental monitoring” OR “environmental pollutants” OR “environmental pollution” OR “Environmental Restoration” OR “Environmental Remediation” OR “Fetal Alcohol Spectrum” OR “forensic toxicology” OR

Chemical	Nitrite
	"hazardous substances" OR hepatotox* OR immunotox* OR "Metabolic Inactivation" OR "LC50" OR "Material Safety Data Sheets" OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR "occupational diseases" OR "persian gulf syndrome" OR Pesticides OR poison* OR poisoning OR "substance-induced psychoses" OR terata* OR terato* OR Teratogenesis OR "Toxic Actions" OR toxic OR "toxicity tests" OR Toxicokinetics OR "Toxicological Phenomena" OR toxicology OR toxif* OR toxig* OR "Toxin-Antitoxin Systems" OR "Hematologic Diseases" OR "Methemoglobinemia" OR "Blue Baby Syndrome")

C.3.30 Pentachlorophenol (CAS# 87-86-5 | DTXSID7021106)

A standard literature search was conducted for pentachlorophenol using the search parameters shown in Table C-40 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-40. Set #1 of Search Strategy for Pentachlorophenol

Chemical	Pentachlorophenol
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/01/22
Synonyms	("2,3,4,5,6-Pentachlorophenol"[tiab] OR "87-86-5"[rn] OR "87-86-5"[tiab] OR "PCP"[tiab] OR "Pentachlorophenol"[mh] OR "Pentachlorophenol"[tiab] OR "Phenol, 2,3,4,5,6-pentachloro-"[tiab] OR "1-Hydroxy-2,3,4,5,6-pentachlorobenzene"[tiab] OR "1-Hydroxypentachlorobenzene"[tiab] OR "Chlorophenasic acid"[tiab] OR "CHLOROPHENATE"[tiab] OR "Dowicide EC 7"[tiab] OR "Dura Treet II"[tiab] OR "Fungifen"[tiab] OR "Grundier Arbezol"[tiab] OR "Lauxtol"[tiab] OR "Liroprem"[tiab] OR "NSC 263497"[tiab] OR "Penchlorol"[tiab] OR "Pentachlorphenol"[tiab] OR "Perchlorophenol"[tiab] OR "Permasan"[tiab] OR "Phenol, pentachloro-"[tiab] OR "Pole topper"[tiab] OR "Pole topper fluid"[tiab] OR "Preventol P"[tiab] OR "Santophen 20"[tiab] OR "Satophen"[tiab] OR "UN 3155"[tiab] OR "Witophen P"[tiab] OR "Woodtreat A"[tiab] OR "DTXSID7021106"[tiab] OR "4-06-00-01025 (Beilstein Handbook Reference)"[tiab] OR "AD 73"[tiab] OR "AI3-00134"[tiab] OR "BRN 1285380"[tiab] OR "Caswell No. 641"[tiab] OR "CCRIS 1663"[tiab] OR "Chem-Penta"[tiab] OR "Chem-Tol"[tiab] OR "Chlon"[tiab] OR "Chlorophen"[tiab] OR "CM 613"[tiab] OR "CP 1309"[tiab] OR "Dow pentachlorophenol DP-2 antimicrobial"[tiab] OR "Dowicide 7"[tiab] OR "Dowicide 7 Antimicrobial"[tiab] OR "Dowicide EC-7"[tiab] OR "Durotox"[tiab] OR "EINECS 201-778-6"[tiab] OR "EP 30 (pesticide)"[tiab] OR "EPA Pesticide Chemical Code 063001"[tiab] OR "Forpen-50 Wood Preservative"[tiab] OR "Glazd penta"[tiab] OR "HSDB 894"[tiab] OR "MB 333"[tiab] OR "NCI-C54933"[tiab] OR "NCI-C55378"[tiab] OR "NCI-C56655"[tiab] OR "Ontrack WE Herbicide"[tiab] OR "Ortho Triox Liquid Vegetation Killer"[tiab] OR "Osmose Wood Preserving Compound"[tiab] OR "PCP (pesticide)"[tiab] OR "Penta"[tiab] OR "Penta Concentrate"[tiab] OR "Penta ready"[tiab] OR "Penta WR"[tiab] OR "Penta-kil"[tiab] OR "Pentachlorofenol"[tiab] OR "Pentachlorophenate"[tiab] OR "Pentachlorophenol, DP-2"[tiab] OR "Pentacon"[tiab] OR "Penwar"[tiab] OR "Peratox"[tiab] OR "Permacide"[tiab] OR "Permagard"[tiab] OR "Permatox DP-2"[tiab] OR "Permatox penta"[tiab] OR "Permite"[tiab] OR "Pol Nu"[tiab] OR "RCRA waste number U242"[tiab] OR "Santophen"[tiab] OR "Sinituho"[tiab] OR "Term-i-trol"[tiab] OR "Thompson's wood fix"[tiab] OR "UNII-D9BSU0SE4T"[tiab] OR "Watershed Wood Preservative"[tiab] OR "Weed and Brush Killer"[tiab] OR "Weedone"[tiab])

C.3.31 Selenium (CAS# 7782-49-2 | DTXSID9021261)

A standard literature search was conducted for selenium using the search parameters shown in Table C-41 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-41. Set #1 of Search Strategy for Selenium

Chemical	Selenium
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/04/22
Synonyms	("7782-49-2"[rn] OR "Selenium"[tiab] OR "B-TRAXIM Se"[tiab] OR "C.I. 77805"[tiab] OR "Selenium (Se)"[tiab] OR "Selsaf 2000"[tiab] OR "UN 2658 (DOT)"[tiab] OR "UN 2658"[tiab] OR "DTXSID9021261"[tiab] OR "Selenium, elemental"[tiab] OR "Caswell No. 732"[tiab] OR "CCRIS 4250"[tiab] OR "CI 77805"[tiab] OR "Colloidal selenium"[tiab] OR "EC 231-957-4"[tiab] OR "EINECS 231-957-4"[tiab] OR "Elemental selenium"[tiab] OR "EPA Pesticide Chemical Code 072001"[tiab] OR "Gray selenium"[tiab] OR "HSDB 4493"[tiab] OR "Selenate"[tiab] OR "Selenium alloy"[tiab] OR "Selenium base"[tiab] OR "Selenium dust"[tiab] OR "Selenium elemental"[tiab] OR "Selenium homopolymer"[tiab] OR "Selenium metallicum"[tiab] OR "Selenium, colloidal"[tiab] OR "UNII-H6241UJ22B"[tiab] OR "Vandex"[tiab] OR "7782-49-2"[tiab] OR "Selenium"[mh] OR “Selenomethionine”[tiab] OR “selenocysteine”[tiab])

C.3.32 Silvex (2,4,5-TP) (CAS# 93-72-1 | DTXSID0021387)

A standard literature search was conducted for silvex using the search parameters shown in Table C-42 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-42. Set #1 of Search Strategy for Silvex

Chemical	Silvex
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/07/22
Synonyms	("DTXSID0021387"[tiab] OR "93-72-1"[rn] OR "93-72-1"[tiab] OR "2-(2,4,5-Trichlorophenoxy)propanoic acid"[tiab] OR "2-(2,4,5-Trichlorophenoxy)propionic acid"[tiab] OR "2,4,5-TP"[tiab] OR "Propanoic acid, 2-(2,4,5-trichlorophenoxy)-"[tiab] OR "Silvex"[tiab] OR "(. + -.)-2-(2,4,5-Trichlorophenoxy)propionic acid"[tiab] OR "2,4,5-TCPPA"[tiab] OR "2,4,5-Trichlorophenoxypropanoic acid"[tiab] OR "2,4,5-Trichlorophenoxypropionic acid"[tiab] OR "Color-Set"[tiab] OR "fenoprop"[tiab] OR "(.+-.)-Fenoprop"[tiab] OR "Fenormone"[tiab] OR "Fruitone T"[tiab] OR "Kurosal G"[tiab] OR "Propionic acid, 2-(2,4,5-trichlorophenoxy)-"[tiab] OR "(.+-.)-Silvex"[tiab] OR "Silvex (2,4,5-TP)"[tiab] OR "Silvi-Rhap"[tiab] OR "Sta-fast"[tiab] OR "TRICHLOROPHENOXYPROPIONIC ACID"[tiab] OR "α-(2,4,5-Trichlorophenoxy)propionic acid"[tiab] OR "(+-)-2-(2,4,5-Trichlorophenoxy)propanoic acid (9CI)"[tiab] OR "(+-)-Fenoprop"[tiab] OR "(+-)-Silvex"[tiab] OR "3-06-00-00721 (Beilstein Handbook Reference)"[tiab] OR "alpha-(2,4,5-Trichlorophenoxy)propionic acid"[tiab] OR "Amchem 2,4,5 TP"[tiab] OR "Amchem 2,4,5-TP"[tiab] OR "Aqua-vex"[tiab] OR "BRN 1985768"[tiab] OR "Caswell No. 739"[tiab] OR "CCRIS 1467"[tiab] OR "Double strength"[tiab] OR "EINECS 202-271-2"[tiab] OR "EPA Pesticide Chemical Code 082501"[tiab] OR "Herbicides, silvex"[tiab] OR "HSDB 686"[tiab] OR "Miller Nu Set"[tiab] OR "Propon"[tiab] OR "RCRA waste number U233"[tiab] OR "UNII-D2HZL58IS3"[tiab])

C.3.33 Styrene (CAS# 100-42-5 | DTXSID2021284)

A standard literature search was conducted for styrene using the search parameters shown in Table C-43 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-43. Set #1 of Search Strategy for Styrene

Chemical	Styrene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/10/22
Synonyms	("DTXSID2021284"[tiab] OR "100-42-5"[tiab] OR "100-42-5"[rn] OR "Benzene, ethenyl-"[tiab] OR "Ethenylbenzene"[tiab] OR "Phenylethylene"[tiab] OR "Styrene"[tiab] OR "Vinylbenzene"[tiab] OR "Benzene ethenyl"[tiab] OR "Benzene,ethenyl-"[tiab] OR "Benzene,ethenyl.."[tiab] OR "Cinnamene"[tiab] OR "NSC 62785"[tiab] OR "Phenethylene"[tiab] OR "Phenylethene"[tiab] OR "Stypol 040-0165"[tiab] OR "STYRENE MONOMER"[tiab] OR "Styrole"[tiab] OR "Styrolene"[tiab] OR "Styropol SO"[tiab] OR "UN 2055"[tiab] OR "Vinylbenzene, Phenylethylene"[tiab] OR "VINYL BENZENE, PHENYLETHYLENE"[tiab] OR "Vinylbenzol"[tiab] OR "AI3-24374"[tiab] OR "Benzene, vinyl-"[tiab] OR "Bulstren K-525-19"[tiab] OR "CCRIS 564"[tiab] OR "EC 202-851-5"[tiab] OR "EINECS 202-851-5"[tiab] OR "Ethylene, phenyl-"[tiab] OR "FEMA No. 3233"[tiab] OR "FEMA Number 3234"[tiab] OR "HSDB 171"[tiab] OR "NCI-C02200"[tiab] OR "UNII-44LJ2U959V"[tiab] OR "Vinyl benzene"[tiab] OR "Styrene"[mh])

C.3.34 Thallium (CAS# 7440-28-0 | DTXSID2036035)

A standard literature search was conducted for thallium using the search parameters shown in Table C-44 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-44. Set #1 of Search Strategy for Thallium

Chemical	Thallium
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/22/22
Synonyms	("7440-28-0"[rn] OR "7440-28-0"[tiab] OR "Thallium"[mh] OR "Thallium"[tiab] OR "Thallium element"[tiab] OR "DTXSID2036035"[tiab] OR "Thallium, elemental"[tiab] OR "EINECS 231-138-1"[tiab] OR "HSDB 4496"[tiab] OR "Ramor"[tiab] OR "Thallium, metallic"[tiab] OR "UNII-AD84R52XLF"[tiab])

C.3.35 Toluene (CAS# 108-88-3 | DTXSID7021360)

The literature search conducted for toluene used the search parameters toxicology filters for PubMed® and Web of Science shown in Table C-45 and Table C-46, respectively.

Table C-45. Set #1 and Set #2 of Search Strategy for Toluene in PubMed

Chemical	Toluene
Assessment for Date Limit	ATSDR (2017b, 10314675)
Search Date Limit	06/01/16
Search Date	03/16/22

Chemical	Toluene
Set #1 (Synonyms)	("108-88-3"[rn] OR "108-88-3"[tiab] OR "Benzene, methyl-"[tiab] OR "Toluene"[mh] OR "Toluene"[tiab] OR "1-Methylbenzene"[tiab] OR "Benzene,methyl"[tiab] OR "Benzene, methyl"[tiab] OR "Methacide"[tiab] OR "Methylbenzene"[tiab] OR "METHYL BENZENE"[tiab] OR "Methylbenzol"[tiab] OR "NSC 406333"[tiab] OR "Phenylmethane"[tiab] OR "TOLOULE OR TOLUOL"[tiab] OR "Toulene"[tiab] OR "EPA Pesticide Chemical Code 080601"[tiab] OR "HSDB 131"[tiab] OR "Methane, phenyl-"[tiab] OR "NCI-C07272"[tiab] OR "RCRA waste number U220"[tiab] OR "Tolu-Sol"[tiab] OR "UNII-3FPU23BG52"[tiab])
Set #2 (Filter)	AND ("Toxicol Sci"[TA] OR (drug-induced abnormalities OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR Chemical and Drug Induced Liver Injury OR chemical hazard release OR Clin Toxicol Phila[TA] OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary, and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Environmental Restoration and Remediation OR Extreme Environments OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR Fetal Alcohol Spectrum Disorders OR OR forensic toxicology OR Global Warming OR hazardous substances OR hepatotox* OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Integumentary System Physiological Phenomena/drug effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR Male Urogenital Diseases/chemically induced[Mesh] OR manufactured materials/adverse effects[Mesh] OR mental disorders/chemically induced[Mesh] OR mutagen* OR mutagenesis OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Organic Chemicals/adverse effects[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR poisoning OR Polycyclic Compounds/adverse effects[Mesh] OR substance-induced psychoses OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR Respiratory Tract Diseases/chemically induced[Mesh] OR Safety-Based Drug Withdrawals OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR Toxicology[TA]))
Limit: Language	AND (English[lang])

Table C-46. Set #1 and Set #2 of Search Strategy for Toluene in WoS

Chemical	Toluene
Assessment for Date Limit	ATSDR (2017b, 10314675)
Search Date Limit	06/01/16
Search Date	03/16/22
Set #1 (Synonyms)	("108-88-3"[rn] OR "108-88-3"[tiab] OR "Benzene, methyl-"[tiab] OR "Toluene"[mh] OR "Toluene"[tiab] OR "1-Methylbenzene"[tiab] OR "Benzene,methyl"[tiab] OR "Benzene, methyl"[tiab] OR "Methacide"[tiab] OR "Methylbenzene"[tiab] OR "METHYL BENZENE"[tiab] OR "Methylbenzol"[tiab] OR "NSC 406333"[tiab] OR "Phenylmethane"[tiab] OR "TOLOULE OR TOLUOL"[tiab] OR "Toulene"[tiab] OR "EPA Pesticide Chemical Code 080601"[tiab] OR "HSDB 131"[tiab] OR "Methane, phenyl-"[tiab] OR "NCI-C07272"[tiab] OR "RCRA waste number U220"[tiab] OR "Tolu-Sol"[tiab] OR "UNII-3FPU23BG52"[tiab])

Chemical	Toluene
Set #2 (Filter)	AND ((“adverse effects” AND (“Biomedical Materials” OR Carbohydrates OR “Chemical Actions” OR “Chemical Uses” OR “Complex Mixtures” OR “Environment Health” OR “Public Health” OR “household products” OR “Pharmaceutical Preparations” OR “Polycyclic Compounds” OR radiotherapy)) OR ((“chemically induced” OR “chemical induced”) AND (“Animal Diseases” OR “Cardiovascular Diseases” OR “Congenital Diseases” OR “Congenital Abnormalities” OR “Hereditary Diseases” OR “Hereditary Abnormalities” OR “Neonatal Diseases” OR “Neonatal Abnormalities” OR “Disorders of Environmental Origin” OR “Environmental Disorders” OR “Urogenital Diseases” OR “Pregnancy Complications” OR “Immune System Diseases” OR “Immune Diseases” OR “mental disorders” OR “Neoplasms” OR “Cancer” OR “Nervous System Diseases” OR “Metabolic Diseases” OR “Pathological Conditions” OR “Pathological Signs” OR “Pathological Symptoms” OR “Respiratory Tract Diseases” OR “Liver injury”)) OR ((“drug effects” OR “drug induced”) AND (“birth weight” OR “Integumentary System Physiological Phenomena” OR “Reproductive Physiological Phenomena” OR “Urinary Physiological Phenomena” OR “liver injury”)) OR “drug-induced abnormalities” OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR “chemical hazard release” OR “chemical induced disorders” OR “Environmental Health” OR “environmental illness” OR “environmental monitoring” OR “environmental pollutants” OR “environmental pollution” OR “Environmental Restoration” OR “Environmental Remediation” OR “Fetal Alcohol Spectrum” OR “forensic toxicology” OR “hazardous substances” OR hepatotox* OR immunotox* OR “Metabolic Inactivation” OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR “occupational diseases” OR poisoning OR “substance-induced psychoses” OR terata* OR terato* OR Teratogenesis OR “Toxic Actions” OR toxic OR “toxicity tests” OR Toxicokinetics OR “Toxicological Phenomena” OR toxicology)

C.3.36 1,2,4-Trichlorobenzene (CAS# 120-82-1 | DTXSID0021965)

A standard literature search was conducted for 1,2,4-trichlorobenzene using the search parameters shown in Table C-47 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-47. Set #1 of Search Strategy for 1,2,4-Trichlorobenzene

Chemical	1,2,4-Trichlorobenzene
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	03/07/22
Synonyms	("120-82-1"[rn] OR "120-82-1"[tiab] OR "1,2,4-Trichlorobenzene"[tiab] OR "1,2,4-Trichlorobenzol"[tiab] OR "1,3,4-Trichlorobenzene"[tiab] OR "Benzene, 1,2,4-trichloro-"[tiab] OR "Hostetex L-PEC"[tiab] OR "NSC 406697"[tiab] OR "unsym-Trichlorobenzene"[tiab] OR "1,2,4-Trichlorbenzol"[tiab] OR "1,2,4-triclorobenceno"[tiab] OR "1,2,5-Trichlorobenzene"[tiab] OR "DTXSID0021965"[tiab] OR "4-05-00-00664 (Beilstein Handbook Reference)"[tiab] OR "AI3-07775"[tiab] OR "BRN 0956819"[tiab] OR "CCRIS 5945"[tiab] OR "EC 204-428-0"[tiab] OR "EINECS 204-428-0"[tiab] OR "HSDB 1105"[tiab])

C.3.37 1,1,1-Trichloroethane (CAS# 71-55-6 | DTXSID0021381)

A standard literature search was conducted for 1,1,1-trichlorobenzene using the search parameters shown in Table C-48 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-48. Set #1 of Search Strategy for 1,1,1-Trichloroethane

Chemical	1,1,1-Trichloroethane
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14
Search Date	02/24/22
Synonyms	("1,1,1-Trichloroethane"[tiab] OR "71-55-6"[rn] OR "71-55-6"[tiab] OR "DTXSID0021381"[tiab] OR "Ethane, 1,1,1-trichloro-"[tiab] OR "Methyl chloroform"[tiab] OR "1,1,1-TRICHLORAETHAN"[tiab] OR "1,1,1-Trichlorethan"[tiab] OR "1,1,1-Trichlorethane"[tiab] OR "1,1,1-tricloroetano"[tiab] OR "Aerothene TT"[tiab] OR "Chlorotene"[tiab] OR "CHLOROTHENE"[tiab] OR "Chlorothene NU"[tiab] OR "Chlorothene SM"[tiab] OR "Chlorothene VG"[tiab] OR "Chlorten"[tiab] OR "Cleanite"[tiab] OR "Ethana NU"[tiab] OR "Genklene LB"[tiab] OR "Inhibisol"[tiab] OR "Methylchloroform"[tiab] OR "Methyltrichloromethane"[tiab] OR "NSC 9367"[tiab] OR "Tafclean"[tiab] OR "Three One A"[tiab] OR "Three One S"[tiab] OR "Trichloroethane, 1,1,1-"[tiab] OR "Trichloromethylmethane"[tiab] OR "Tricloroethane"[tiab] OR "UN 2831"[tiab] OR "α-Trichloroethane"[tiab] OR "1,1,1-TCE"[tiab] OR "4-01-00-00138 (Beilstein Handbook Reference)"[tiab] OR "AI3-02061"[tiab] OR "Baltana"[tiab] OR "BRN 1731614"[tiab] OR "Caswell No. 875"[tiab] OR "CCRIS 1290"[tiab] OR "Chloroform, methyl-"[tiab] OR "Chlorothene, inhibited"[tiab] OR "Dowclene LS"[tiab] OR "EC 200-756-3"[tiab] OR "EINECS 200-756-3"[tiab] OR "EPA Pesticide Chemical Code 081201"[tiab] OR "F 140a"[tiab] OR "HCC 140a"[tiab] OR "HSDB 157"[tiab] OR "ICI-CF 2"[tiab] OR "NCI-C04626"[tiab] OR "RCRA waste number U226"[tiab] OR "Solvent 111"[tiab] OR "Trichloro-1,1,1-ethane"[tiab] OR "Trichloroethane"[tiab] OR "UNII-113C650IR1"[tiab])

C.3.38 Toxaphene (CAS# 8001-35-2 | DTXSID7021368)

A standard literature search was conducted for toxaphene using the search parameters shown in Table C-49 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-49. Set #1 of Search Strategy for Toxaphene

Chemical	Toxaphene
Assessment for Date Limit	EPA (2018c, 5373923)
Search Date Limit	07/01/17
Search Date	03/09/22
Synonyms	("8001-35-2"[rn] OR "8001-35-2"[tiab] OR "Alltox"[tiab] OR "Anatox"[tiab] OR "Camphechlor"[tiab] OR "Camphene, octachloro-"[tiab] OR "M 5055"[tiab] OR "PChK"[tiab] OR "PChK (insecticide)"[tiab] OR "PKhF"[tiab] OR "Toxaphene"[mh] OR "Toxaphene"[tiab] OR "UN 2761"[tiab] OR "Camphochlor"[tiab] OR "Canfeclor"[tiab] OR "Chlorinated camphene"[tiab] OR "Estonox"[tiab] OR "Geniphene"[tiab] OR "Hercules 3956"[tiab] OR "Kamfochlor"[tiab] OR "Melipax"[tiab] OR "Phenacide"[tiab] OR "Phenatox"[tiab] OR "Polychloro-2,2-dimethyl-3-methylidenebicyclo[2.2.1]heptane"[tiab] OR "Polychlorocamphene"[tiab] OR "Strobane T"[tiab] OR "toxafeno"[tiab] OR "Toxakil"[tiab] OR "Toxaphen"[tiab] OR "DTXSID7021368"[tiab] OR "Agricide Maggot Killer"[tiab] OR "Agricide maggot killer (F)"[tiab] OR "Agro-Chem Brand Torbidan 28"[tiab] OR "Agro-Chem Brand Toxaphene 6E"[tiab] OR "Agsco toxaphene"[tiab] OR "Agway toxaphene 6E"[tiab] OR "Alltex"[tiab] OR "Attac 4-2"[tiab] OR "Attac 4-4"[tiab] OR "Attac 6"[tiab] OR "Attac 6-3"[tiab] OR "Attac 8"[tiab] OR "Camphechlore"[tiab] OR "Camphofene huileux"[tiab] OR "Caswell No. 861"[tiab] OR "CCRIS 600"[tiab] OR "Chem-Phene"[tiab] OR "Chlorocamphene"[tiab] OR "Clor Chem T-590"[tiab] OR "Clor Chem T-590 Insecticide"[tiab] OR "Compound 3956"[tiab] OR "Coopertox"[tiab] OR "Cotton-Tox MP 82"[tiab] OR "Crestoxo"[tiab]

Chemical	Toxaphene
	OR "Cristoxo 90"[tiab] OR "Dr Roger's TOX-ENE"[tiab] OR "EINECS 232-283-3"[tiab] OR "ENT 9,735"[tiab] OR "EPA Pesticide Chemical Code 080501"[tiab] OR "Fasco-terpene"[tiab] OR "Felco/Land O'Lakes Toxaphene"[tiab] OR "Grower Service Toxaphene 6E"[tiab] OR "Grower Service Toxaphene MP"[tiab] OR "Gy-phene"[tiab] OR "Hercules Toxaphene Emulsifiable Concentrate"[tiab] OR "HSDB 1616"[tiab] OR "Latka 3956"[tiab] OR "Motox"[tiab] OR "NCI-C00259"[tiab] OR "NSC 406917"[tiab] OR "NSC 8932"[tiab] OR "Octachlorocamphene"[tiab] OR "Penphene"[tiab] OR "Polychlorcamphene"[tiab] OR "RCRA waste number P123"[tiab] OR "Red Top Toxaphene 8 Spray"[tiab] OR "Rigo Toxaphene 8"[tiab] OR "Royal Brand Bean Tox 82"[tiab] OR "Security Motox 63 cotton spray"[tiab] OR "Security Tox-MP cotton spray"[tiab] OR "Security Tox-Sol-6"[tiab] OR "Strobane T-90"[tiab] OR "Strobane-T"[tiab] OR "Synthetic 3956"[tiab] OR "Toxadust"[tiab] OR "Toxaphene (technical)"[tiab] OR "Toxaphene 8 EC"[tiab] OR "Toxaphene 8 Emulsifiable Insecticide"[tiab] OR "Toxaphene 90-10"[tiab] OR "Toxaphene E-8"[tiab] OR "Toxon 63"[tiab] OR "Toxyphen"[tiab] OR "UNII-9924JQ4D5J"[tiab] OR "Vertac 90%"[tiab])

C.3.39 Vinyl chloride (CAS# 75-01-4 | DTXSID8021434)

A standard literature search was conducted for vinyl chloride using the search parameters shown in Table C-50 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-50. Set #1 of Search Strategy for Vinyl chloride

Chemical	Vinyl chloride
Assessment for Date Limit	ATSDR (2006d, 2991431); ATSDR (2016, 10489757)
Search Date Limit	01/01/15
Search Date	03/25/22
Synonyms	("75-01-4"[rn] OR "75-01-4"[tiab] OR "Chloroethene"[tiab] OR "EC No.: 200-831-0"[tiab] OR "Ethene, chloro-"[tiab] OR "Vinyl chloride"[mh] OR "Vinyl chloride"[tiab] OR "1-Chloroethene"[tiab] OR "1-Chloroethylene"[tiab] OR "Chloroethylene"[tiab] OR "ETHYLENE, CHLORO-"[tiab] OR "MONOCHLOROETHYLENE"[tiab] OR "UN 1086"[tiab] OR "VINYLCHLORID"[tiab] OR "Vinyl chloride monomer"[tiab] OR "Vinyl C monomer"[tiab] OR "DTXSID8021434"[tiab] OR "4-01-00-00700 (Beilstein Handbook Reference)"[tiab] OR "BRN 1731576"[tiab] OR "CCRIS 621"[tiab] OR "Chlorethene"[tiab] OR "Chlorethylene"[tiab] OR "EC 200-831-0"[tiab] OR "EINECS 200-831-0"[tiab] OR "Ethylene monochloride"[tiab] OR "HSDB 169"[tiab] OR "Monochloroethene"[tiab] OR "Monovinyl chloride"[tiab] OR "RCRA waste number U043"[tiab] OR "Trovidur"[tiab] OR "UNII-WD06X94M2D"[tiab] OR "Vinyl chlorine"[tiab] OR "Vinylchloride"[tiab])

C.3.40 Xylenes (total) (CAS# 1330-20-7 | DTXSID2021446)

A standard literature search was conducted for xylenes using the search parameters shown in Table C-51 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-51. Set #1 of Search Strategy for Xylenes

Chemical	Xylenes
Assessment for Date Limit	EPA (2016c, 6557097)
Search Date Limit	12/01/14

Chemical	Xylenes
Search Date	02/17/22
Synonyms	("1330-20-7"[rn] OR "Entellan New"[tiab] OR "Xylene"[tiab] OR "Xylene (mixture)"[tiab] OR "Xylenes"[tiab] OR "Xylol"[tiab] OR "ZEP-RD"[tiab] OR "Benzene, dimethyl"[tiab] OR "Benzene, dimethyl-"[tiab] OR "Benzene,dimethyl-(mixed)"[tiab] OR "Dimethyl benzene"[tiab] OR "DIMETHYLBENZENE"[tiab] OR "xileno, mezcla de isomeros, puro"[tiab] OR "Xylene, melange d'isomeres, pur"[tiab] OR "DTXSID2021446"[tiab] OR "AI3-02209-X"[tiab] OR "BRN 1901563"[tiab] OR "Caswell No. 906"[tiab] OR "CCRIS 903"[tiab] OR "EC 215-535-7"[tiab] OR "EINECS 215-535-7"[tiab] OR "EPA Pesticide Chemical Code 086802"[tiab] OR "HSDB 4500"[tiab] OR "Methyl toluene"[tiab] OR "Methyltoluene"[tiab] OR "NCI-C55232"[tiab] OR "RCRA waste number U239"[tiab] OR "UN 1307"[tiab] OR "UNII-D856J1047R"[tiab] OR "Violet 3"[tiab] OR "4-05-00-00951 (Beilstein Handbook Reference)"[tiab] OR "Xylenes"[mh] OR "1330-20-7"[tiab] OR “ortho xylene”[tiab] OR “meta xylene”[tiab] OR “para xylene”[tiab])

C.4 Search Strategies for TSCA Chemicals

C.4.1 Asbestos (fiber > 10 micrometers) (CAS# 1332-21-4 | DTXSID4023888)

A standard literature search was conducted for asbestos using the search parameters shown in Table C-52 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-52. Set #1 of Search Strategy for Asbestos

Chemical	Asbestos
Assessment for Date Limit	EPA (2021d, 10565930)
Search Date Limit	04/01/20
Search Date	09/09/22
Synonyms	("1332-21-4"[rn] OR "1332-21-4"[tiab] OR "Amiante"[tiab] OR "Asbestos"[mh] OR "Asbestos"[tiab] OR "Asbestos, exposure"[tiab] OR "Asbestos, fibers"[tiab] OR "Asbestos (firable form)"[tiab] OR "Asbestos substitutes"[tiab] OR "Asbestos synthetic fibers"[tiab] OR "HPO (mineral)"[tiab] OR "Sepiolex 3"[tiab] OR "Sepiolex 5"[tiab] OR "SM 1 (mineral)"[tiab] OR "DTXSID4023888"[tiab] OR "Amianthus"[tiab] OR "Asbest"[tiab] OR "Asbestos dust"[tiab] OR "Asbestos fiber"[tiab] OR "Asbestos fibers"[tiab] OR "Asbestos fibre"[tiab] OR "Ascarite"[tiab] OR "AT 7-1"[tiab] OR "BK 6-20"[tiab] OR "BP 3-50"[tiab] OR "BP 5-65"[tiab] OR "Calidria HPP"[tiab] OR "Calidria R-G 244"[tiab] OR "Carey 4T"[tiab] OR "Caswell No. 061"[tiab] OR "CCRIS 56"[tiab] OR "Chlorobestos 25"[tiab] OR "EPA Pesticide Chemical Code 099301"[tiab] OR "FAPM 410-120"[tiab] OR "Ferodo C3C"[tiab] OR "Fibrous grunerite"[tiab] OR "HSDB 511"[tiab] OR "K 6-20"[tiab] OR "M 3-60"[tiab] OR "M 4-5"[tiab] OR "M 5-60"[tiab] OR "M 6-40"[tiab] OR "Mountain cork"[tiab] OR "Mountain leather"[tiab] OR "Mountain wood"[tiab] OR "MTM"[tiab] OR "NCI C08991"[tiab] OR "P 5-50"[tiab] OR "P 5-50 (mineral)"[tiab] OR "SM 2 (mineral)"[tiab])

C.4.2 Carbon tetrachloride (CAS# 56-23-5 | DTXSID8020250)

A standard literature search was conducted for carbon tetrachloride using the search parameters shown in Table C-53 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-53. Set #1 of Search Strategy for Carbon Tetrachloride

Chemical	Carbon Tetrachloride
Assessment for Date Limit	EPA (2020d, 7697236)
Search Date Limit	03/01/16
Search Date	09/28/22
Synonyms	("56-23-5"[rn] OR "56-23-5"[tiab] OR "AI3-04705"[tiab] OR "Benzinoform"[tiab] OR "Carbon chloride (CCl4)"[tiab] OR "Carbon tet"[tiab] OR "Carbon tetrachloride"[tiab] OR "Carbon tetrachloride"[mh] OR "Carbona"[tiab] OR "Caswell No. 164"[tiab] OR "CC m0"[tiab] OR "CCRIS 123"[tiab] OR "DTXSID8020250"[tiab] OR "EC 200-262-8"[tiab] OR "EINECS 200-262-8"[tiab] OR "ENT 27164"[tiab] OR "ENT 4,705"[tiab] OR "EPA Pesticide Chemical Code 016501"[tiab] OR "Fasciolin"[tiab] OR "Flukoids"[tiab] OR "Freon 10"[tiab] OR "Halon 1040"[tiab] OR "HSDB 53"[tiab] OR "Methane tetrachloride"[tiab] OR "Methane, tetrachloro-"[tiab] OR "Necatorina"[tiab] OR "Necatorine"[tiab] OR "NSC 97063"[tiab] OR "Perchloromethane"[tiab] OR "R 10"[tiab] OR "R 10 (Refrigerant)"[tiab] OR "RCRA waste number U211"[tiab] OR "Tetrachlorocarbon"[tiab] OR "Tetrachloromethane"[tiab] OR "Tetrafinol"[tiab] OR "Tetraform"[tiab] OR "Tetrasol"[tiab] OR "UN 1846"[tiab] OR "UNII-CL2T97X0V0"[tiab] OR "Univerm"[tiab] OR "Univerm"[tiab] OR "Vermoestricid"[tiab])

C.4.3 1,2-Dichlorobenzene (o-Dichlorobenzene) (CAS# 95-50-1 | DTXSID6020430)

A standard literature search was conducted for 1,2-dichlorobenzene using the search parameters shown in Table C-54 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-54. Set #1 of Search Strategy for 1,2-Dichlorobenzene

Chemical	1,2-Dichlorobenzene
Assessment for Date Limit	EPA (2020q, 10565931)
Search Date Limit	05/01/18
Search Date	09/23/22
Synonyms	("1,2-Dichlorobenzene"[tiab] OR "95-50-1"[rn] OR "Benzene, 1,2-dichloro-"[tiab] OR "o-dichlorobenzene"[tiab] OR "1,2-Dichlorbenzol"[tiab] OR "1,2-diclorobenceno"[tiab] OR "Benzene, o-dichloro-"[tiab] OR "Cloroben"[tiab] OR "Dilatin DB"[tiab] OR "Dowtherm E"[tiab] OR "NSC 60644"[tiab] OR "O-DICHLORBENZOL"[tiab] OR "o-Dichlorobenzol"[tiab] OR "ortho-Dichlorobenzene"[tiab] OR "UN 1591"[tiab] OR "DTXSID6020430"[tiab] OR "2-Dichlorobenzene"[tiab] OR "AI3-00053"[tiab] OR "Caswell No. 301"[tiab] OR "CCRIS 1360"[tiab] OR "Chloroben"[tiab] OR "DCB"[tiab] OR "Dichlorobenzene, ortho, liquid"[tiab] OR "Dilantin DB"[tiab] OR "Dizene"[tiab] OR "EC 202-425-9"[tiab] OR "EINECS 202-425-9"[tiab] OR "EPA Pesticide Chemical Code 059401"[tiab] OR "HSDB 521"[tiab] OR "NCI-C54944"[tiab] OR "o-Dichlor benzol"[tiab] OR "Orthodichlorobenzene"[tiab] OR "Orthodichlorobenzol"[tiab] OR "Special termite fluid"[tiab] OR "Termitkil"[tiab] OR "UNII-6PJ93I88XL"[tiab])

C.4.4 1,4-Dichlorobenzene (p-Dichlorobenzene) (CAS# 106-46-7 | DTXSID1020431)

A standard literature search was conducted for 1,4-dichlorobenzene using the search parameters shown in Table C-55 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-55. Set #1 of Search Strategy for 1,4-Dichlorobenzene

Chemical	1,4-Dichlorobenzene
Assessment for Date Limit	EPA (2020f, 10565932)
Search Date Limit	09/01/18
Search Date	09/23/22
Synonyms	("106-46-7" OR "106-46-7" OR "1,4-Dichlorobenzene" OR "Benzene, 1,4-dichloro-" OR "p-dichlorobenzene" OR "1,4-Dichlorbenzol" OR "Benzene, p-dichloro-" OR "BENZENE, P-DICHLORO" OR "Di-chloricide" OR "Dichlorobenzene, para-" OR "Dichlorocide" OR "NSC 36935" OR "para-Dichlorobenzene" OR "Paradichlorobenzene" OR "Paradow" OR "Paramoth" OR "p-Chlorophenyl chloride" OR "P-DICHLORBENZOL" OR "Persia-Perazol" OR "Santochlor" OR "UN 1592" OR "DTXSID1020431" OR "4-Dichlorobenzene" OR "1,4-Dichloorbenzeen" OR "1,4-Diclorobenzene" OR "AI3-00050" OR "AI3-0050" OR "Caswell No. 632" OR "CCRIS 307" OR "Dichlorobenzene" OR "EC 203-400-5" OR "EINECS 203-400-5" OR "EPA Pesticide Chemical Code 061501" OR "Evola" OR "Globol" OR "HSDB 523" OR "NCI-C54955" OR "Para crystals" OR "Paracide" OR "Paradi" OR "Paranuggets" OR "RCRA waste number U070" OR "RCRA waste number U071" OR "RCRA waste number U072" OR "UNII-D149TYB5MK")

C.4.5 1,2-Dichloroethane (1,2-DCA) (CAS# 107-06-2 | DTXSID6020438)

A standard literature search was conducted for 1,2-dichloroethane using the search parameters shown in Table C-56 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-56. Set #1 of Search Strategy for 1,2-Dichloroethane

Chemical	1,2-Dichloroethane
Assessment for Date Limit	EPA (2020r, 10565935)
Search Date Limit	09/01/18
Search Date	09/27/22
Synonyms	("107-06-2"[rn] OR "107-06-2"[tiab] OR "1,2-Dichloroethane"[tiab] OR "1.2-Ethylene dichloride"[tiab] OR "Brocide"[tiab] OR "Dichlor-Mulsion"[tiab] OR "Ethane, 1,2-dichloro-"[tiab] OR "Ethylene chloride"[tiab] OR "Glycol dichloride"[tiab] OR "1,2-Bichloroethane"[tiab] OR "1,2-DICHLORAETHAN"[tiab] OR "1,2-Dichlorethan"[tiab] OR "1,2-Dichlorethane"[tiab] OR "1,2-dicloroetano"[tiab] OR "1,2-Ethylene dichloride"[tiab] OR "Dichloroethane, 1,2-"[tiab] OR "Dutch liquid"[tiab] OR "ETHANE, 1,2-DICHLORO"[tiab] OR "Ethane dichloride"[tiab] OR "ETHYLENE DICHLORIDE"[tiab] OR "sym-Dichloroethane"[tiab] OR "UN 1184"[tiab] OR "α,β-Dichloroethane"[tiab] OR "DTXSID6020438"[tiab] OR "AI3-01656"[tiab] OR "alpha,beta-Dichloroethane"[tiab] OR "Borer sol"[tiab] OR "Caswell No. 440"[tiab] OR "CCRIS 225"[tiab] OR "DCE"[tiab] OR "Destruxol borer-sol"[tiab] OR "Di-chlor-mulsion"[tiab] OR "Dichloremulsion"[tiab] OR "Dichloroethylene"[tiab] OR "Dutch oil"[tiab] OR "EC 203-458-1"[tiab] OR "EDC (halocarbon)"[tiab] OR "EINECS 203-458-1"[tiab] OR "ENT 1,656"[tiab] OR "EPA Pesticide Chemical Code 042003"[tiab] OR "Freon 150"[tiab] OR "HCC 150"[tiab] OR "HSDB

Chemical	1,2-Dichloroethane
	65"[tiab] OR "NCI-C00511"[tiab] OR "RCRA waste number U077"[tiab] OR "RY Dichloro-1,2-ethane"[tiab] OR "UNII-55163IJI47"[tiab])

C.4.6 trans-1,2-Dichloroethylene (CAS# 156-60-5 | DTXSID7024031)

A standard literature search was conducted for trans-1,2-dichloroethylene using the search parameters shown in Table C-57 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-57. Set #1 of Search Strategy for trans-1,2-Dichloroethylene

Chemical	trans-1,2-Dichloroethylene
Assessment for Date Limit	EPA (2020h, 10565934)
Search Date Limit	07/01/18
Search Date	09/29/22
Synonyms	("156-60-5"[rn] OR "156-60-5"[tiab] OR "(1E)-1,2-Dichloroethene"[tiab] OR "(E)-1,2-Dichloroethene"[tiab] OR "(E)-1,2-Dichloroethylene"[tiab] OR "Ethene, 1,2-dichloro-, (1E)-"[tiab] OR "Ethene, 1,2-dichloro-, (E)-"[tiab] OR "trans-1,2-Dichloroethene"[tiab] OR "trans-1,2-Dichloroethylene"[tiab] OR "1,2-trans-Dichloroethene"[tiab] OR "1,2-trans-Dichloroethylene"[tiab] OR "Ethylene, 1,2-dichloro-, (E)-"[tiab] OR "Ethylene, 1,2-dichloro-, trans-"[tiab] OR "NSC 60512"[tiab] OR "trans-Dichlorethylen"[tiab] OR "trans-dichloroethylene"[tiab] OR "trans-dicloroetileno"[tiab] OR "Vertrel CCA"[tiab] OR "DTXSID7024031"[tiab] OR "4-01-00-00709 (Beilstein Handbook Reference)"[tiab] OR "AI3-28786"[tiab] OR "BRN 1420761"[tiab] OR "CCRIS 2505"[tiab] OR "EC 205-860-2"[tiab] OR "EINECS 205-860-2"[tiab] OR "HCC 1130t"[tiab] OR "HSDB 6361"[tiab] OR "R 1130t"[tiab] OR "RCRA waste number U079"[tiab] OR "trans-Acetylene dichloride"[tiab] OR "UNII-41799BI61U"[tiab])

C.4.7 Di(2-ethylhexyl)phthalate (CAS# 117-81-7 | DTXSID5020607)

A standard literature search was conducted for di(2-ethylhexyl)phthalate using the search parameters shown in Table C-58 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-58. Set #1 of Search Strategy for Di(2-ethylhexyl)phthalate

Chemical	Di(2-ethylhexyl)phthalate
Assessment for Date Limit	EPA (2020k, 10565938)
Search Date Limit	09/01/18
Search Date	09/28/22
Synonyms	("117-81-7"[rn] OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester"[tiab] OR "2-Ethylhexyl phthalate"[tiab] OR "Bis(2-ethylhexyl) benzene-1,2-dicarboxylate"[tiab] OR "Bis-(2-ethylhexyl)-phthalate"[tiab] OR "DEHP"[tiab] OR "Di-(2-ethylhexyl) phthalate"[tiab] OR "Di(2-ethylhexyl) phthalate"[tiab] OR "di(alpha-Ethylhexyl) phthalate"[tiab] OR "1,2-Benzedicarboxylic acid, bis(2-ethyl-hexyl) ester"[tiab] OR "1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester"[tiab] OR "1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester"[tiab] OR "1,2-Benzenedicarboxylic acid,bis(2-ethylhexylester)"[tiab] OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate"[tiab] OR "Bis(2-ethylhexyl) o-phthalate"[tiab] OR "Bis(2-ethylhexyl)phthalat"[tiab] OR "bis(2-ethylhexyl)

Chemical	Di(2-ethylhexyl)phthalate
	phthalate"[tiab] OR "Bis(2-ethylhexyl)phthalate"[tiab] OR "Bisoflex 81"[tiab] OR "Bisoflex DOP"[tiab] OR "Corflex 400"[tiab] OR "Di-2-ethylhexlphthalate"[tiab] OR "Di-2-ethylhexyl phthalate"[tiab] OR "Di(2-ethylhexyl)phthalate"[tiab] OR "DI-2-ETHYLHEXYL-PHTHALATE"[tiab] OR "Diacizer DOP"[tiab] OR "Diethylhexyl phthalate"[tiab] OR "Di(isooctyl) phthalate"[tiab] OR "Ergoplast FDO"[tiab] OR "Ergoplast FDO-S"[tiab] OR "ETHYLHEXYL PHTHALATE"[tiab] OR "Eviplast 80"[tiab] OR "Eviplast 81"[tiab] OR "Fleximel"[tiab] OR "Flexol DOD"[tiab] OR "Flexol DOP"[tiab] OR "Garbeflex DOP-D 40"[tiab] OR "Good-rite GP 264"[tiab] OR "Hatco DOP"[tiab] OR "Jayflex DOP"[tiab] OR "Kodaflex DEHP"[tiab] OR "Kodaflex DOP"[tiab] OR "Monocizer DOP"[tiab] OR "NSC 17069"[tiab] OR "Palatinol AH"[tiab] OR "Palatinol AH-L"[tiab] OR "PHTHALATE, BIS(2-ETHYLHEXYL)"[tiab] OR "Phthalic acid, bis(2-ethylhexyl) ester"[tiab] OR "PHTHALIC ACID, BIS(2-ETHYLHEXYL)ESTER"[tiab] OR "Phthalic acid di(2-ethylhexyl) ester"[tiab] OR "Pittsburgh PX 138"[tiab] OR "Plasthall DOP"[tiab] OR "Reomol D 79P"[tiab] OR "Sansocizer DOP"[tiab] OR "Sansocizer R 8000"[tiab] OR "Sconamoll DOP"[tiab] OR "Staflex DOP"[tiab] OR "Truflex DOP"[tiab] OR "Vestinol AH"[tiab] OR "Vinycizer 80"[tiab] OR "Vinycizer 80K"[tiab] OR "Witcizer 312"[tiab] OR "DTXSID5020607"[tiab] OR "4-09-00-03181 (Beilstein Handbook Reference)"[tiab] OR "AI3-04273"[tiab] OR "BRN 1890696"[tiab] OR "Caswell No. 392K"[tiab] OR "CCRIS 237"[tiab] OR "Celluflex DOP"[tiab] OR "Compound 889"[tiab] OR "Di(2-ethylhexyl) orthophthalate"[tiab] OR "Di(2-ethylhexyl)orthophthalate"[tiab] OR "Dioctyl phthalate"[tiab] OR "EC 204-211-0"[tiab] OR "EINECS 204-211-0"[tiab] OR "EPA Pesticide Chemical Code 295200"[tiab] OR "Etalon"[tiab] OR "Etalon (plasticizer)"[tiab] OR "Flexol Plasticizer DOP"[tiab] OR "Hatcol DOP"[tiab] OR "Hercoflex 260"[tiab] OR "HSDB 339"[tiab] OR "Mollan O"[tiab] OR "NCI-C52733"[tiab] OR "Nuoplaz DOP"[tiab] OR "Octoil"[tiab] OR "Pittsburgh PX-138"[tiab] OR "Platinol AH"[tiab] OR "Platinol DOP"[tiab] OR "PX-138"[tiab] OR "RC Plasticizer DOP"[tiab] OR "RCRA waste number U028"[tiab] OR "Reomol DOP"[tiab] OR "Sicol 150"[tiab] OR "UNII-C42K0PH13C"[tiab] OR "Vinicizer 80"[tiab] OR "117-81-7"[tiab] OR "Diethylhexyl phthalate"[mh])

C.4.8 Ethylene dibromide (CAS# 106-93-4 | DTXSID3020415)

A standard literature search was conducted for ethylene dibromide using the search parameters shown in Table C-59 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-59. Set #1 of Search Strategy for Ethylene Dibromide

Chemical	Ethylene Dibromide
Assessment for Date Limit	EPA (2020j, 10565937)
Search Date Limit	09/01/18
Search Date	09/09/22
Synonyms	("106-93-4"[rn] OR "1,2-Dibromoethane"[tiab] OR "Ethane, 1,2-dibromo-"[tiab] OR "Ethylene dibromide"[tiab] OR "Aadibroom"[tiab] OR "Bromofume"[tiab] OR "Dayfum W-85"[tiab] OR "Dowfume W 8"[tiab] OR "Dowfume W 85"[tiab] OR "Edabrom"[tiab] OR "Ethylene bromide"[tiab] OR "Glycol dibromide"[tiab] OR "Iscobrome D"[tiab] OR "Sanhyuum"[tiab] OR "Soilbrom"[tiab] OR "Soilfume"[tiab] OR "sym-Dibromoethane"[tiab] OR "UN 1605"[tiab] OR "α,β-Dibromoethane"[tiab] OR "α,ω-Dibromoethane"[tiab] OR "DTXSID3020415"[tiab] OR "1,2-Ethylene dibromide"[tiab] OR "4-01-00-00158 (Beilstein Handbook Reference)"[tiab] OR "AI3-15349"[tiab] OR "alpha,beta-Dibromoethane"[tiab] OR "alpha,omega-Dibromoethane"[tiab] OR "BRN 0605266"[tiab] OR "Caswell No. 439"[tiab] OR "CCRIS 295"[tiab] OR "Celmide"[tiab] OR "Dowfume 40"[tiab] OR "Dowfume EDB"[tiab] OR "Dowfume W-100"[tiab] OR "Dowfume W-8"[tiab] OR "Dowfume W-85"[tiab] OR "Dowfume W-90"[tiab] OR "E-D-Bee"[tiab] OR "EC 203-

Chemical	Ethylene Dibromide
	444-5"[tiab] OR "EDB"[tiab] OR "EDB-85"[tiab] OR "EINECS 203-444-5"[tiab] OR "ENT 15,349"[tiab] OR "EPA Pesticide Chemical Code 042002"[tiab] OR "Fumo-gas"[tiab] OR "HSDB 536"[tiab] OR "Kopfume"[tiab] OR "NCI-C00522"[tiab] OR "Nefis"[tiab] OR "Nephis"[tiab] OR "Pestmaster edb-85"[tiab] OR "RCRA waste number U067"[tiab] OR "Soilbrom-100"[tiab] OR "Soilbrom-40"[tiab] OR "Soilbrom-85"[tiab] OR "Soilbrom-90"[tiab] OR "Soilbrom-90EC"[tiab] OR "Unifume"[tiab] OR "UNII-1N41638RNO"[tiab] OR "106-93-4"[tiab] OR "Ethylene dibromide"[mh])

C.4.9 Tetrachloroethylene (CAS# 127-18-4 | DTXSID2021319)

A standard literature search was conducted for tetrachloroethylene using the search parameters shown in Table C-60 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-60. Set #1 of Search Strategy for Tetrachloroethylene

Chemical	Tetrachloroethylene
Assessment for Date Limit	EPA (2020l, 7697272)
Search Date Limit	03/01/16
Search Date	01/25/22
Synonyms	("127-18-4"[RN] OR "Ethene, 1,1,2,2-tetrachloro-"[TIAB] OR "Ethene, 1,1,2,2-tetrachloro-"[TIAB] OR "PERC"[TIAB] OR "TCE"[TIAB] OR "Tetrachloroethene"[TIAB] OR "Tetrachloroethylene"[TIAB] OR "1,1,2,2-Tetrachloroethene"[TIAB] OR "1,1,2,2-TETRACHLOROETHYLENE"[TIAB] OR "Ankilostin"[TIAB] OR "Asahi Perchlor"[TIAB] OR "Didakene"[TIAB] OR "Dilatin PT"[TIAB] OR "Ethene, tetrachloro-"[TIAB] OR "Ethylene tetrachloride"[TIAB] OR "Ethylene, tetrachloro-"[TIAB] OR "Fedal-Un"[TIAB] OR "NSC 9777"[TIAB] OR "PERCHLORAETHYLEN"[TIAB] OR "Perchlorethylene"[TIAB] OR "Perchloroethene"[TIAB] OR "PERCHLOROETHYLENE"[TIAB] OR "Perclene"[TIAB] OR "Perklone"[TIAB] OR "Tetrachlorethylen"[TIAB] OR "Tetrachlorethylene"[TIAB] OR "tetracloroetileno"[TIAB] OR "Tetraguer"[TIAB] OR "Tetraleno"[TIAB] OR "Tetropil"[TIAB] OR "UN 1897"[TIAB] OR "DTXSID2021319"[TIAB] OR "4-01-00-00715 (Beilstein Handbook Reference)"[TIAB] OR "AI3-01860"[TIAB] OR "Antisol 1"[TIAB] OR "BRN 1361721"[TIAB] OR "Carbon bichloride"[TIAB] OR "Carbon dichloride"[TIAB] OR "Caswell No. 827"[TIAB] OR "CCRIS 579"[TIAB] OR "Dow-per"[TIAB] OR "EC 204-825-9"[TIAB] OR "EINECS 204-825-9"[TIAB] OR "ENT 1,860"[TIAB] OR "EPA Pesticide Chemical Code 078501"[TIAB] OR "HSDB 124"[TIAB] OR "NCI-C04580"[TIAB] OR "PCE"[TIAB] OR "Perawin"[TIAB] OR "Perchlor"[TIAB] OR "Perclene D"[TIAB] OR "Percosolv"[TIAB] OR "Percosolve"[TIAB] OR "Persec"[TIAB] OR "RCRA waste number U210"[TIAB] OR "Tetlen"[TIAB] OR "Tetracap"[TIAB] OR "Tetrachloroethylene (IUPAC)"[TIAB] OR "Tetralex"[TIAB] OR "Tetravec"[TIAB] OR "Tetroguer"[TIAB] OR "UNII-TJ904HH8SN"[TIAB] OR "127-18-4"[TIAB] OR "Tetrachloroethylene"[Mesh])

C.4.10 1,1,2-Trichloroethane (CAS# 79-00-5 | DTXSID5021380)

A standard literature search was conducted for 1,1,2-trichloroethane using the search parameters shown in Table C-61 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-61. Set #1 of Search Strategy for 1,1,2-Trichloroethane

Chemical	1,1,2-Trichloroethane
Assessment for Date Limit	EPA (2020n, 10565933)
Search Date Limit	09/01/18
Search Date	09/27/22
Synonyms	("1,1,2-Trichloroethane" OR "1,2,2-Trichloroethane" OR "79-00-5" OR "79-00-5" OR "Ethane, 1,1,2-trichloro-" OR "Ethane trichloride" OR "β-Trichloroethane" OR "1,1,2-TRICHLORAETHAN" OR "1,1,2-Trichlorethan" OR "1,1,2-tricloroetano" OR "Ethane, 1,1,2-trichloro" OR "NSC 405074" OR "Vinyltrichloride" OR "Vinyl trichloride" OR "DTXSID5021380" OR "1,1,2-Trichlorethane" OR "4-01-00-00139 (Beilstein Handbook Reference)" OR "beta-Trichloroethane" OR "BRN 1731726" OR "Caswell No. 875A" OR "CCRIS 602" OR "EC 201-166-9" OR "EINECS 201-166-9" OR "EPA Pesticide Chemical Code 081203" OR "HSDB 1412" OR "NCI-C04579" OR "RCRA waste number U227" OR "RCRA waste number U359" OR "UNII-28E9ERN9WU")

C.4.11 Trichloroethylene (CAS# 79-01-6 | DTXSID0021383)

A standard literature search was conducted for trichloroethylene using the search parameters shown in Table C-62 and toxicology filters for PubMed® and Web of Science shown in Table C-1 and Table C-2, respectively.

Table C-62. Set #1 of Search Strategy for Trichloroethylene

Chemical	Trichloroethylene
Assessment for Date Limit	EPA (2020o, 5176430)
Search Date Limit	03/01/16
Search Date	09/30/22
Synonyms	("Trichloroethylene"[Mesh] OR "Trichloroethylene"[tiab] OR "79-01-6"[rn] OR "79-01-6"[tiab] OR "DTXSID0021383"[tiab] OR "1,1,2-Trichloroethene"[tiab] OR "Ethene, 1,1,2-trichloro-"[tiab] OR "Ethene, 1,1,2-trichloro-"[tiab] OR "Ethylene, trichloro-"[tiab] OR "TCE"[tiab] OR "TCE (chlorohydrocarbon)"[tiab] OR "1,1,2-Trichloroethylene"[tiab] OR "Acetylene trichloride"[tiab] OR "Algylen"[tiab] OR "Anamenth"[tiab] OR "Chlorilen"[tiab] OR "Chlorylen"[tiab] OR "Densinfluat"[tiab] OR "Ethene, trichloro-"[tiab] OR "Ethinyl trichloride"[tiab] OR "Ethylene trichloride"[tiab] OR "Germalgene"[tiab] OR "LPS HDX Heavy Duty Degreaser"[tiab] OR "Narcogen"[tiab] OR "Narkosoid"[tiab] OR "Threthylen"[tiab] OR "Threthylene"[tiab] OR "Trethylene"[tiab] OR "TRICHLORAETHYLEN"[tiab] OR "Trichloran"[tiab] OR "Trichloren"[tiab] OR "Trichlorethylen"[tiab] OR "TRICHLOROETHENE"[tiab] OR "Triclene"[tiab] OR "tricloroetileno"[tiab] OR "Trielene"[tiab] OR "Trielin"[tiab] OR "Trieline"[tiab] OR "Trilene"[tiab] OR "UN 1710"[tiab] OR "Westrosol"[tiab] OR "1,1-Dichloro-2-chloroethylene"[tiab] OR "1,2,2-Trichloroethylene"[tiab] OR "1-Chloro-2,2-dichloroethylene"[tiab] OR "4-01-00-00712 (Beilstein Handbook Reference)"[tiab] OR "AI3-00052"[tiab] OR "Benzinol"[tiab] OR "BRN 1736782"[tiab] OR "Caswell No. 876"[tiab] OR "CCRIS 603"[tiab] OR "Cecolene"[tiab] OR "Dow-tri"[tiab] OR "Dukeron"[tiab] OR "EC 201-167-4"[tiab] OR "EINECS 201-167-4"[tiab] OR "EPA Pesticide Chemical Code 081202"[tiab] OR "F 1120"[tiab] OR "Fleck-flip"[tiab] OR "Flock FLIP"[tiab] OR "Fluate"[tiab] OR "HSDB 133"[tiab] OR "Lanadin"[tiab] OR "Lethurin"[tiab] OR "NCI-C04546"[tiab] OR "Nialk"[tiab] OR "NSC 389"[tiab] OR "Perm-A-chlor"[tiab] OR "Petzinol"[tiab] OR "Philex"[tiab] OR "R 1120"[tiab] OR "RCRA waste number U228"[tiab] OR "Tri-clene"[tiab] OR "Tri-plus"[tiab] OR "Tri-plus M"[tiab] OR "Triasol"[tiab] OR "Trichloraethylenum"[tiab] OR "Trichlorethylenum"[tiab] OR "Trichloroethylene (IUPAC)"[tiab] OR "Trichloroethylenum"[tiab] OR "Trilen"[tiab] OR "Trilene TE-141"[tiab] OR "Trimar"[tiab] OR "UNII-290YE8AR51"[tiab] OR "Vestrol"[tiab] OR "Vitran"[tiab])