United States Environmental Protection Agency

Six-Year Review 3 - Health Effects Assessment for Existing Chemical and Radionuclide National Primary Drinking Water Regulations - Summary Report

This document is intended to support U.S. EPA's third Six-Year Review of existing national primary drinking water regulations. The data presented in this document reflect literature searches through December 2014 and health risk assessments completed by December 2015.

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LIST OF ABBREVIATIONS/ACRONYMS

ADAF- Age- Dependent Adjustment Factor

ADWR - Aircraft Drinking Water Rule

ATSDR- Agency for Toxic Substances and Disease Registry

BMD10- Benchmark Dose at a 10% response

BMDL- Lower confidence limit on the benchmark dose (mg/kg/day)

BW- Body Weight

CalEPA- California Environmental Protection Agency

CCRIS- Chemical Carcinogenesis Research Information System

CICADS- Concise International Chemical Assessment Documents

CSF- Cancer Slope Factor

DART- Developmental and Reproductive Toxicology

DEHP- Di(2-ethylhexyl) phthalate

DWEL- Drinking Water Equivalent Level

DWI- Drinking Water Intake

ED10- Effective Dose corresponding to a 10% increase in an adverse effect

FAO- Food and Agriculture Organization of the United Nations

FQPA- Food Quality Protection Act

HSDB- Hazardous Substances Data Bank

IARC- International Agency for Research on Cancer

I-Intake from drinking water

IPCS/EHC- International Programme on Chemical Safety/Environmental Health Criteria

IRIS- Integrated Risk Information System

JECFA- Joint Expert Committee on Food Additives

JMPR- Joint FAO/WHO Meeting on Pesticide Residues

LED10- 95% Lower Confidence Limit on the Effective Dose

LOAEL- Lowest Observed Adverse Effect Level (mg/kg/day)

LT1 – Long-Term 1 Enhanced Surface Water Treatment Rule

LT2 – Long-Term 2 Enhanced Surface Water Treatment Rule

MCL- Maximum Contaminant Level

MCLG- Maximum Contaminant Level Goal

MF- Modifying Factor

MOA- Mode of Action

MOE- Margin of Exposure

MRLs- Minimal Risk Levels

NAS- National Academy of Sciences

NCWSs- Non-Community Water Systems

NDWAC- National Drinking Water Advisory Council

NHANES- National Health and Nutrition Examination Survey

NIEHS- National Institute of Environmental Health Sciences

NOAEL- No Observed Adverse Effect Level (mg/kg/day)

NPDWR- National Primary Drinking Water Regulation

NTP- National Toxicology Program

OPP- Office of Pesticide Programs

OPP- U.S. EPA Office of Pesticide Programs

ORIA- U.S. EPA Office of Radiation and Indoor Air

OW- U.S. EPA Office of Water

PHG- Public Health Goal

POD- Point of Departure

PQL- Practical Quantitation Level

RED- Reregistration Eligibility Decisions

RfD- Reference Dose

RSC- Relative Source Contribution

SD- Standard Deviation

SDWA- Safe Drinking Water Act

U.S. EPA- United States Environmental Protection Agency

UF- Uncertainty factor

VOCs- Volatile Organic Compounds

WHO- World Health Organization

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SUMMARY REPORT

1. INTRODUCTION

The 1996 amendments to the Safe Drinking Water Act (SDWA), Section 1412(b)(9), require the United States Environmental Protection Agency (U.S. EPA) to review existing National Primary Drinking Water Regulation (NPDWR) every six years and determine which, if any, are candidates for revision. The SDWA Amendments also specify that any revision of a 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 "revise" or "take no action") to existing NPDWRs based on changes in health effects and/or analytical or technological feasibility that have occurred since the regulations were promulgated.

In response to this mandate, U.S. EPA developed a Protocol for the Review of Existing National Primary Drinking Water Regulations (U.S. EPA, 2002a; 2003e) based on recommendations of the National Drinking Water Advisory Council (NDWAC, U.S. EPA, 2000a) and input from stakeholders representing a wide variety of interest groups. U.S. EPA has updated this protocol for the third review effort (U.S. EPA, 2016d). The protocol outlines the approach to be 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 3 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 Cl2], chlorine [as Cl2], chlorine dioxide, chlorite, total trihalomethanes and haloacetic acids). Information on these contaminants is evaluated in a separate document developed by EPA: Technical Support Document titled "Technical Support Document for Disinfectants/Disinfection Byproducts Regulations Under Six-Year Review 3" (USEPA, 2016h).

In addition, turbidity is also not evaluated in this report because it is not a chemical pollutant and it is covered in a separate document (U.S. EPA, 2016f and 2016g). Finally, five microbial contaminants/groups are analyzed under Surface Water Treatment Rule (SWTR), Interim Enhanced SWTR, LT1/LT2 Enhanced SWTR (Cryptosporidium, Giardia lamblia, Heterotrophic plate count, Legionella, Viruses) separately under 'Technical Support Document for Microbial Contaminant Regulations Under Six-Year Review 3' (U.S. EPA, 2016f) and under 'Technical Support Document for Long-Term 2 Regulation Under Six-Year Review 3' (U.S. EPA, 2016g).

1.1 Background

The Agency completed its first Six-Year Review (referred to here as "Six-Year Review 1") in July 2003 (U.S. EPA, 2002b; 2003a). In the Six-Year Review 1, EPA evaluated the information available at that time on the key elements of the review process for sixty-eight (68) chemical contaminants covered under various NPDWRs. The assessment of health effects for those sixty-eight (68) chemicals was presented in the Six-Year Review, Chemical Contaminants – Health Effects Technical Support Document (U.S. EPA, 2003f). Five chemicals 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. These five chemicals were beryllium, 1,1-dichloroethylene, lindane, oxamyl, and picloram. The Six-Year Review 1 health assessment also identified three chemical contaminants (cyanide, di(2-ethylhexyl) adipate and thallium) as high priority for reevaluation because of reproductive and/or developmental information based on the literature search and new assessments available at that time. Fluoride was also identified as a candidate for reevaluation because of information on dental, bone and cancer effects. In completing Six-Year Review 1, the Agency determined that it was not appropriate to revise any of the sixty-eight (68) chemicals NPDWRs considered at that time (U.S. EPA, 2003a).

The agency completed the health effects review for the second Six-Year Review in October 2009 (U.S. EPA, 2010f; 2009c) (referred to here as "Six-Year Review 2"). Under Six-Year Review 2, the health assessments of seventy-one (71) chemicals were reviewed, including sixty-six (66) of the sixty-eight (68) chemicals from Six-Year Review 1. Lead and copper were not included under Six-Year Review 2 because of ongoing efforts initiated in 2006 to revise the Lead and Copper Rule. However, five chemicals not considered during Six-Year Review 1 (arsenic; uranium; combined radium [226 and 228]; alpha particle emitters; and beta particle and photon emitters), for which new regulations had been promulgated, were considered during Six-Year Review 2.

During Six-Year Review 2, new EPA health assessments were identified that could impact 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)). It should be noted that the identification of chemicals qualifying for revision was independent of other considerations (e.g., analytical and treatment technology, occurrence data) that may have influenced the final selection of contaminants to be revised. EPA also identified five contaminants (chromium, nitrate, nitrite, selenium, and 1,2,4-trichlorobenzene) for which new literature was available supporting 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, 2009c).

Considering analytical methods, technology and other factors along with health assessments during Six-Year Review 2, EPA identified four NPDWR chemical contaminants as candidates for revision. The four NPDWRs were: acrylamide, epichlorohydrin, tetrachloroethylene, and trichloroethylene.

1.2 Six-Year Review 3

The decision-making process of the Six-Year Review 3 protocol was essentially the same as that implemented during Six-Year Review 1 and Six-Year Review 2, however a modification to the protocol was included in this cycle of review. For the Six-Year Review 1 and Six-Year Review 2, only EPA assessments were evaluated for their potential impact on maximum contaminant level goal (MCLG) revisions. The non-EPA assessments (e.g., Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), and Health Canada) were reviewed but not included in the consideration of potential revisions to the MCLG. For the Six-Year Review 3, these non-EPA assessments were taken into consideration as the basis for potential MCLG revisions, as appropriate. The EPA Integrated Risk Information System (IRIS) and the Office of Pesticide Programs (OPP) became the predominant sources for reference dose and cancer slope factors for this update. For a few contaminants, however, more recent toxicity assessments from federal, state and international agencies provided the assessments that identified potential revisions to MCLGs.

After identifying and documenting all available toxicity values, EPA selected the toxicity values for non-carcinogenic and carcinogenic effects that could potentially change an existing MCLG. A more current toxicological assessment from a source other than EPA was selected when these assessments introduced new science (e.g., the toxicity value was based on a newer principal study) or used a more current approach for dose-response quantification. Final decisions about potential changes to an MCLG take into account information beyond consideration of toxicity (e.g., occurrence and exposure, treatment technologies, analytical methods).

Beginning with the National Interim Primary Drinking Water Regulations (U.S. EPA, 1976), MCLGs have been typically derived using an adult body weight of 70 kg and drinking water intake of 2 L per day. The body weight assumption of 70 kg, was supported by the mean bodyweight of adults from the NHANES III database (1988–1994) and a 1989 study conducted by the National Cancer Institute (Section 4.3.1 in U.S.EPA, 2000b). The drinking water intake rate of 2 L/day was also first selected for use in development of the National Interim Primary Drinking Water Regulations (U.S. EPA, 1976) considering the data available at the time. Support to this value is 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 (USEPA 2000b, section 4.3.2.1). Updates to the drinking water intake and body weight parameters are provided in EPA's *Exposure Factors Handbook* (U.S. EPA, 2011a) supporting a revision for the 90th percentile consumers only tap water intake to 2.5 L per day and the mean adult body weight to 80 kg, respectively. This review focuses primarily on the impact of new toxicity data in evaluating changes to MCLGs, and thus comparisons have been made using the older body weight and tap-water intake assumptions. The net effect of adjusting these values would be less than a 9% reduction in the MCLGs. In a few cases (e.g., carbofuran, oxamyl), where the most recent toxicity values were derived for infants and children, the potential MCLGs were calculated based on children's body weight and water intake for the first year of life.

Under Six-Year Review 3, the initial review identified 12 Chemical Phase Rule NPDWRs that were being considered as part of ongoing or pending regulatory actions. These 12 NPDWRs included:

- Eight chemicals (benzene, carbon tetrachloride, 1,2-dichloroethane, dichloromethane, 1,2-dichloropropane, tetrachloroethylene, trichloroethylene, and vinyl chloride) are being evaluated as part of the Group Regulation of Carcinogenic Volatile Organic Compounds (cVOCs) (U.S. EPA, 2011b; U.S. EPA, 2014b).
- Copper and lead are being evaluated in an ongoing effort to revise the Lead-Copper Rule/NSDWR (U.S. EPA, 1991f and 2007a)
- Acrylamide and epichlorohydrin were identified as candidates for revisions in Six-Year Review 2 (U.S. EPA, 2010f) and were pending regulatory revision. For the technical analysis for these two contaminants, see *Support Document for Third Six Year Review of Drinking Water Regulations for Acrylamide and Epichlorohydrin* (U.S. EPA, 2016e).

EPA determined that for 19 NPDWRs, a USEPA health effects assessment is currently in process or planned by the Office of Research and Development program Integrated Risk Information System (IRIS), the Office of Pesticide Programs (OPP), the Office of Radiation and Indoor Air (ORIA), the Office of Water (OW), or the National Academy of Sciences (assessment commissioned by USEPA). Therefore, additional health effects reviews for those chemicals as part of Six-Year Review 3 were not necessary. The 19 chemicals (List A) are identified in Table 1.

Table 1: List A Chemicals - Health Effects Assessment in Process or Nominated for Health Assessment

Alpha/photon emitters	Di(2-ethylhexyl) phthalate (DEHP)	Nitrite
Arsenic, inorganic	1, 2 Dichlorobenzene	Polychlorinated biphenyls (PCBs)
Atrazine	1,4 Dichlorobenzene	Radium (226, 228)
Benzo(a)pyrene (PAH)	Ethylbenzene	Simazine
Beta/photon emitters	Glyphosate	Uranium
Cadmium	Mercury	
Chromium (VI) as part of total Cr)	Nitrate	

EPA's OPP is conducting reviews of atrazine, simazine, and glyphosate in Registration Review.

EPA's Office of Research and Development is reviewing (or plans to review) inorganic arsenic, benzo(a)pyrene, chromium (VI), ethylbenzene, cadmium, di(2-ethylhexyl) phthalate (DEHP), mercury, nitrate, nitrite, 1,2-dichlorobenzene, 1,4-dichlorobenzene, PCBs and uranium through the IRIS program. Inorganic arsenic, benzo(a)pyrene, chromium, and PCBs are currently

under review and the remaining chemicals are included in the current IRIS multiyear plan. (U.S. EPA, 2015). For the purpose of the Six-Year Review 3, these chemicals were considered as having ongoing assessments and placed on List A.

Following the promulgation of the final radionuclides rule (U.S. EPA, 2000c), additional information became available on the adverse health effects of ionizing radiation (including alpha particle emitters; beta particle and photon emitters; and combined radium (226 and 228)), as well as for the mechanisms that cause cellular and molecular damage. In light of this new information, EPA's ORIA has begun the process of revising its radiation risk methodology to incorporate the new data, (U.S. EPA, 2007b, 2007c, 2007d).

The following forty-two (42) chemicals, identified as List B (Table 2) underwent a more detailed review including the evaluation of effects and risk-based values from government agencies and publications from the primary literature. This document summarizes the results of the review of the health effects component of the Six-Year Review 3 effort for the chemicals identified below.

Table 2: List B Chemicals – Evaluated for Health Effects to Determine the Potential Impact on the MCLG

Alachlor	Ethylene Dibromide (EDB;1,2-Dibromoethane)
Antimony*	Fluoride
Asbestos*	Heptachlor
Barium	Heptachlor epoxide
Beryllium*	Hexachlorobenzene
Carbofuran	Hexachlorocyclopentadiene
Chlordane	Lindane (gamma-hexachloro-cyclohexane)
Chlorobenzene (Monochlorobenzene)	Methoxychlor
Cyanide, free*	Oxamyl (Vydate)
2,4-D (2,4-Dichlorophenoxy Acetic Acid)	Pentachlorophenol*
Dalapon (2,2-Dichloropropionic Acid)	Picloram
1,2-Dibromo-3-chloropropane (DBCP)	Selenium
1,1-Dichloroethylene	Styrene*¶
cis-1,2-Dichloroethylene*	Thallium*
trans-1,2-Dichloroethylene*	Toluene
Di(2-ethylhexyl) adipate (DEHA)*	Toxaphene
Dinoseb	2,4,5-TP (Silvex; 2,4,5 Trichlorophenoxypropionic Acid)
Dioxin*	1,2,4-Trichlorobenzene
Diquat	1,1,1-Trichloroethane
Endothall	1,1,2-Trichloroethane
Endrin	Xylenes (total)

*Not reviewed during Six-Year Review 2 because of ongoing assessments

¶ Included in IRIS Multi-year agenda (U. S. EPA 2015), but is included in List B based on a Cal-EPA Assessment

1.3 Objectives and Report Organization

The first objective of the review was to identify new quantitative and qualitative health information that could indicate a possible basis for revising the MCLG when supported by occurrence data and technological feasibility. The second objective of the review was to identify chemicals that might warrant a new formal Agency health effects assessment or further follow-up and evaluation based on the availability of significant new health information identified through the literature searches.

Section 2 provides an overview of U.S. EPA health effects assessment methods, for both carcinogens and non-carcinogens, that are relevant to the health effects assessments conducted under this Six-Year Review.

Section 3 describes the overall process implemented to evaluate any new health effects for chemicals considered in this Six-Year Review.

Section 4 presents the results of the health effects review, including the identification of those chemicals for which OW identified new health risk assessment that suggested a possible change to the current MCLG could be considered.

Section 5 provides an overall summary of this document.

2. OVERVIEW OF U.S. EPA HEALTH EFFECTS ASSESSMENT METHODS

2.1 Non-carcinogens

For chemicals exhibiting a threshold for toxic effects, U.S. EPA establishes the MCLG based on an oral reference dose (RfD). The MCL is the same as the MCLG in cases where it is technically feasible based on quantitation levels and treatment technology, and can be achieved at a cost commensurate with the benefits achieved. A change in the RfD could lead to a change in the MCLG. 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 derived as follows:

$$\text{RfD (mg/kg/day)} = \frac{\text{NOAEL or LOAEL or BMDL}}{\text{UF}}$$

where:

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

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

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

UF = uncertainty factor

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; 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 there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

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 in cases where the study doses have a different level of change than the one that defines an effect as adverse. 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. If a study has greater-than-usual sensitivity, then a lower BMR can be used, although the benchmark dose 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. In the absence of any other data on the adverse response level, a change in the mean equal to one control standard deviation (1SD) from the control mean is generally used (U.S. EPA, 2000d; 2012a).

BMD modeling is an alternative 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. In practice, the BMDL is often used as an alternative to the NOAEL as a point of departure in recent noncancer risk assessments. Selecting BMRs involves making judgments about the statistical and biological characteristics of the dataset (e.g., quantal versus continuous) and about the applications for which the resulting BMDs/BMDLs will be used.

Uncertainty Factors (UF): The NOAELs, LOAELs or BMDLs selected for deriving the RfD can be determined from animal or human data. In calculating an RfD, the NOAEL, LOAEL or BMDL is divided by a composite uncertainty factor (UF). An UF is a product of several uncertainty factors accounting for variation in sensitivity among members of the human population, extrapolation from animal data to humans, extrapolation from a LOAEL to a NOAEL, extrapolation of subchronic data to lifetime, and database deficiencies. Each individual UF presented below may range between 1 and 10 to account for the uncertainty introduced either by variability or the absence of information. The specific magnitude of the value is based upon a combination of scientific evidence and professional judgment (U.S EPA, 2002c).

Some older assessments also used a modifying factor (MF) in the calculation of the overall UF. Discontinuation of the MF was recommended in 2002 (U.S. EPA, 2002b), and the IRIS glossary states that the MF was discontinued in 2004. The magnitude of the MF reflected the scientific uncertainties of the study and database not explicitly treated with standard uncertainty factors

(e.g., the completeness of the overall database). Current practice is to address those uncertainties in the database uncertainty factor. A MF was greater than zero and less than or equal to 10, and the default value for the MF was 1. Based on the EPA guidance for RfD determination, the total UF may not exceed 3000 (U.S. EPA, 2002c).

The following paragraphs describe the component uncertainty factors, based on current U.S. EPA guidance for use of uncertainty factors for IRIS and similar programs. 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 an RfD for nutritionally essential elements, taking into account 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 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 for 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 results of studies of human exposure 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 approaches are used in extrapolating from the animal data (U.S. EPA, 1994c). Chemical-specific data can also be used to adjust this factor, when adequate data are available. A factor of 1 can be used when valid results are obtained 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 responds.

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 in a case where the dose response 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 study NOAEL or when benchmark dose 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 (NOAEL or LOAEL) in humans or experimental animals are used in the absence of useful long-term human or animal data. A factor of 3 may be used for intermediate data, such as when some data on chronic exposures are available but the study did not evaluate some of the parameters shown to be affected in studies of shorter 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 less-than-chronic results are used, if it is known that the subchronic study is more sensitive than any chronic studies, or that the critical 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 the systemic toxicity studies, the key consideration 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, 2002c). Note that U.S. EPA did not generally use the UF_D prior to approximately 1998. The exception was the where database deficiencies were addressed with the use of a modifying factor, as discussed above. After 1998, the UF_D was adopted by the IRIS program, but 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 U.S. EPA based on incomplete databases might be 3- to 10-fold lower if current uncertainty factor guidelines were followed. This is the case for several regulated chemicals that have since been reevaluated by IRIS or the Office of Pesticide Programs (OPP) resulting in the addition of a UF_D to the Total UF for the same critical effects and point of departure as the one used for the regulation.

2.2 Carcinogens

U.S. EPA's health effects assessment for carcinogens involves assessing both the weight of evidence for carcinogenicity and the potency. This section presents U.S. EPA's guidance for assessing carcinogens as it has evolved from the 1986 guidelines (U.S. EPA, 1986i) through the final 2005 guidelines (U.S. EPA, 2005a, 2005e).

2.2.1 Classifications

Under the 1986 guidelines, the qualitative assessment began with a separate evaluation of the animal and human data, identifying the data as sufficient, limited, inadequate, "no data," or "no evidence of carcinogenicity." The animal and human data were combined with other available data for an overall weight-of-evidence evaluation, using the following groups:

Group A – Human carcinogen

Group B – Probable human carcinogen

B1 "limited" evidence of carcinogenicity based on epidemiology data, and

B2 "sufficient" evidence of carcinogenicity from animal data, but "inadequate" or "no data" in humans

Group C – Possible human carcinogen

Group D – Not classifiable as to human carcinogenicity

Group E – Evidence of non-carcinogenicity for humans

Proposed revisions to the 1986 cancer guidelines were released in 1996 and 1999 (U.S. EPA, 1996, 1999) as interim guidelines and both revisions were applied to official final U.S. EPA assessments. Other interim cancer guidelines were published but not used in official final U.S. 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 mode of action (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 2.2.2), 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

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 MOA[1]. 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 screening-level health review for Six-Year Review 3 chemicals are based only on the Agency's most recent available formal risk assessments. Note that U.S. EPA cancer assessments conducted between 1996 (following publication of the proposed guidelines) and 2001, when the Agency published a Federal Register notice (*60 FR 59594*) 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.

2.2.2 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, the POD is the lowest dose that is adequately supported by the data. The ED10 (the dose corresponding to a 10% increase in tumors), and the LED10 (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.

[1] 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.

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, 2005e), 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 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, 1996, 1999) 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 U.S. 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[2] for carcinogenesis or the tumor response.

2.3 How U.S. EPA Sets the MCLG and MCL

Because the identification of contaminants for possible revision based on health effects is dependent on whether or not the MCLG could change, a brief explanation of the derivation of the MCLG is warranted. 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 MCL is the maximum permissible level of a contaminant in water that is 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 cost onto consideration and technical factors such as the minimal reporting level of the analytical method and treatment technology limitations.

As discussed in the next two sections, there are different approaches used to establish MCLGs for carcinogens and non-carcinogens.

2.3.1 Non-carcinogens

For non-carcinogens, the MCLG is derived from the RfD, which was discussed in Section 2.1. From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined. A DWEL is a drinking water lifetime exposure level, assuming 100% exposure from that medium,

[2] 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.

at which adverse, non-carcinogenic health effects would not be expected to occur. The DWEL is derived as follows:

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

where:

BW = Body Weight (70 kg for adults, 10 kg for children[3])

DWI = Drinking water intake (2 L/day for adults, 1 L/day for children[3]).

The MCLG is then derived by considering other known or potential sources of exposure, using the relative source contribution (RSC) factor.

MCLG (mg/L) = DWEL x RSC

The RSC from drinking water is based on actual exposure data, or, if data are not available, a value of 20% is assumed for effects based on lifetime exposure. This allows 80% of the total exposure to come from sources other than drinking water, such as exposure from food, inhalation, or dermal contact. For the few MCLGs based on adverse effects related to exposure in children, an RSC of 100% was usually applied because the source of exposure for the critical study was drinking water. In assessments completed after the EPA (2000b) RSC decision tree was published in the Human Health Ambient Water Quality Criteria Methodology, a maximum RSC value of 80% allows for potential unidentified sources even when data from other sources are available.

2.3.2 Carcinogens

For drinking water contaminants regulated prior to the 1996 SDWA, OW followed a three-category regulatory cancer classification system (Categories I, II, or III). These categories specify decisions as to 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.

U.S. EPA also used the six alphanumeric categories (A, B1, B2, C, D, and E) of the 1986 cancer guidelines (U.S. EPA, 1986i) in establishing MCLGs. The six-group classification system is often equated to the three-category system in the NPDWR Federal Register announcements. Table 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

[3] The 70 kg body weight and consumers only drinking water intake (90th percentile) of 2L/day were used for most currently regulated chemicals. The comparable values in the EPA (2011a) Exposure Factors Handbook are 80 Kg and 2.5 L/day. The values for children (a one year infant) have also changed. For children, the normalized drinking water intakes per unit body weight over the first year of life is 0.15L/Kg based on the 90th percentile of drinking water consumption and the mean body weight for age groups, birth to <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months rather than the 0.1 ratio used for earlier assessments.

approach, as described in the next section, along with an additional risk management safety factor of 1 to10. If a chemical is placed into Group D or E (Category III), the MCLG was derived using the RfD approach as described in the next section. The methodology used under this approach for establishing MCLGs for chemicals with varying degrees of evidence of carcinogenicity is summarized in Table 3.

A generally similar approach applies to chemicals with cancer assessments developed under more recent U.S. EPA guidelines. The MCLG is generally set at zero for chemicals with a descriptor of *carcinogenic to humans or likely to be carcinogenic to humans.* For a descriptor of *suggestive evidence of carcinogenic potential,* the RfD approach is used.

Table 3: U.S. EPA Three-Category Approach and Corresponding 1986 Cancer Classification System

Three-category approach for establishing MCLGs	Corresponding five-group classification system of 1986 cancer guidelines
MCLG generally set at zero	
Category I: **Known or probable human carcinogens: Strong evidence of carcinogenicity** Sufficient human or animal evidence of carcinogenicity.	**Generally Group A or B:** **A: Human carcinogen** Sufficient evidence from epidemiological studies to support a causal association. **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.
MCLG based on the RfD with an additional safety factor of up to 10 to account for possible carcinogenicity, 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.	**Generally Group C:** **Possible human carcinogen** Limited evidence of carcinogenicity in animals in the absence of human data.
MCLG established using the RfD approach	
Category III: **Inadequate or no evidence of carcinogenicity in animals**	**Group D or Group E:** **D: Not classifiable as to human carcinogenicity** Inadequate human and animal evidence of carcinogenicity, or no data available. **E: Evidence of non-carcinogenicity for humans** No evidence of carcinogenicity in two different animal species, or in both epidemiological and animal studies.

2.4 Key Differences in Human Health Assessment Methods Between U.S. EPA 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. Notable among these are the ATSDR, CalEPA, the World Health Organization (WHO), Health Canada, and NAS. To provide context to that review, key differences between the human health assessment methods of these other organizations and those of U.S. 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 U.S. 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, U.S. 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. For cancer effects, ATSDR cites the cancer classification of National Toxicology Program (NTP), EPA and International Agency for Research on Cancer (IARC) in the toxicological profiles. 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.

Cal EPA 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, Cal EPA 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 uncertainty factor of 3000 may be utilized, with intrahuman variability of up to 30x compared to 10x by U.S. 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. Cal EPA uses a default RSC of 20%, similar to the approach of U.S. EPA, but uses other data-derived values more frequently than does U.S. EPA.

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.

Health Canada 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 considered "essentially negligible," which Health Canada 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 U.S. EPA's RfD methodology is used (U.S. EPA, 2002c). For calculating water concentrations, default values of 70 kg body weight, 1.5 L water intake per day, and a 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), Health Canada employs a multi-route exposure approach to estimate the relative contribution of the inhalation and dermal exposures during showering and bathing. Using this approach, litre-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.

3. PROCESS FOR EVALUATING CHEMICALS FOR THE SIX-YEAR REVIEW 3

3.1 Identification of List A Chemicals (19) For Which The Health Effect Assessment is in Process or That Are Nominated For Health Assessment

These 19 List A chemicals in Table 1 have an ongoing U.S. EPA health assessment in process or have been nominated for a health assessment (as of 12/2015). The review of the List A chemicals/radionuclides was limited to evaluation of available non-cancer and cancer assessments from the following sources: EPA OW, IRIS, ORIA, and OPP Reregistration Eligibility Decisions (RED), to determine if there were new data that should be considered during the Six-Year Review 3. In addition, qualitative and quantitative descriptions of the toxic and cancer effects from U.S. EPA documents for which external review versions are available were also reviewed, with the understanding that these external-peer-review-ready assessments are subject to further changes. No additional literature search was conducted for these chemicals.

For eight List A chemicals (cadmium, 1,2-dichlorobenzene, 1,4-dichlorobenzene, nitrate, nitrite, mercury, DEHP and uranium), an initial literature search was initially conducted and a preliminary evaluation of the literature was completed. Subsequent to these literature searches the 2015 IRIS Multi-Year Agenda announced the intention to conduct updated assessments for the 8 chemicals (U.S. EPA, 2015). These chemicals were consequently considered as having ongoing assessments and placed on List A.

3.2 Literature Search Process for the List B Chemicals (42)

In the case of the List B chemicals a more comprehensive evaluation was performed, including evaluation of effects and risk-based values from published health effects or risk assessments, and evaluation of the primary literature. The cutoff date for the initial search of the primary literature and EPA and other health agencies assessments was December 2014. Because some of the health assessments identified in the initial search were draft, an updated search of EPA and other agency health was performed with a cutoff date of December 2015.

EPA and other health agency authoritative reviews/assessments undertaken by IRIS, OPP, ATSDR, the National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), CalEPA, WHO, Concise International Chemical Assessment Documents (CICADS), International Programme on Chemical Safety/Environmental Health Criteria (IPCS/EHC), IARC, Health Canada, Joint Expert Committee on Food Additives (JECFA), and Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues (JMPR) were included in the searches.

Literature searches were conducted to identify publications from the primary literature to supplement the information in the authoritative reviews. The following databases were searched: TOXLINE, MEDLINE®, Developmental and Reproductive Toxicology (DART®), Chemical Carcinogenesis Research Information System (CCRIS), and Hazardous Substances Data Bank (HSDB). The dates covered by the literature search were determined on an individual chemical basis, to ensure that the literature was adequately captured, but to avoid unnecessary duplication of work done in the authoritative reviews. In general, searches covered posting dates from 2008 (one year before the Six-Year Review 2 was finalized) through December 2014. However, if there was a recent IRIS, OPP, OW, or ATSDR document, the searches began 2 years before publication date of the latest toxicity assessment from IRIS/OPP/OW and 3 years before the publication date of any ATSDR Toxicological Profile. Several chemicals which had an assessment underway during Six-Year Review 2 and were on List A, are on List B for Six-Year Review 3. These chemicals (listed in page 4 with asterisk), did not have supplemental searching during Six-Year Review 3 to cover the gap in search dates during the Six-Year Review 1 to Six-Year Review 2 interval.

The searches and screening of the literature were intended to capture the health effects data related to (1) systemic toxicity and carcinogenicity (including MOA and genotoxicity studies) and for (2) reproductive and developmental toxicity. The search terms were very broad, based on the chemical name, synonyms, and CAS number. Studies with a possible impact on the assessment (i.e., new health outcomes, different NOAEL or LOAEL, mode of action information, etc.) were retrieved and reviewed; other studies of interest were noted based on the information presented in the abstract. After identifying new literature and more currently available assessments, EPA identified toxicity values for non-carcinogenic and carcinogenic effects that could change an existing MCLG. A more current toxicological assessment from a source other than EPA was selected when these assessments introduced new science (e.g., the toxicity value was based on a newer principal study) or used a more current methodological approaches (e.g., BMDL). During the Six-Year Review 3 Review, the recent non-EPA assessments were selected for four contaminants (e.g., methoxychlor, selenium, styrene and 1,2,4-trichlorobenzene).

3.3 Screening Process for List B Chemicals

For the 42 List B chemicals which are not the subject of an ongoing assessment by U.S. EPA, a more comprehensive evaluation was done, including evaluation of effects and risk-based values from risk assessment sources, and evaluation of the primary literature. Literature searches on these chemicals were conducted as discussed above in Section 3.2. Newly identified studies that appeared relevant to the assessment of noncancer, cancer, or reproductive/developmental effects were obtained and screened for the possible impact of new data on current assessments.

U.S. EPA OW Drinking Water Criteria Documents serve as the basis for current regulations (with the exception of arsenic, and radionuclides). Toxicity values from more current assessments completed by the following U.S. EPA Offices or other organizations were evaluated to determine if there was new information that could change the existing MCL/MCLG:

- U.S. EPA Integrated Risk Information System (IRIS)
- U.S. EPA Office of Pesticide Programs (OPP)
- U.S. EPA Office of Radiation and Indoor Air (ORIA)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- California EPA Public Health Goals (CalEPA)
- World Health Organization (WHO)
    - Drinking Water Guidelines (WHO)
    - WHO's Concise International Assessment Documents (CICADs)
    - International Programme on Chemical Safety – Environmental Health Criteria Documents (IPCS, EHC)
- Food and Agriculture Organization of the United Nations (FAO)/WHO
    - Joint Meeting on Pesticide Residues (JMPR)
    - Joint Expert Committee on Food Additives (JECFA)
- Health Canada
- National Academy of Sciences (NAS)
- International Agency for Research on Cancer (IARC)
- National Institute of Environmental Health Sciences (NIEHS) Report on Carcinogens (RoC)
    - National Toxicology Program (NTP)

Based on the availability of new data identified in the literature search and information from existing assessments, recommendations were made regarding the potential for U.S. EPA OW to update its MCLG based on the health effects data alone.

4. RESULTS

4.1 Findings for List A Chemicals with Ongoing EPA Assessments

As of December 31, 2015, 19 List A chemicals were the subject of ongoing EPA assessments and therefore, the Agency is not recommending any changes to the MCLGs for them at this time. The IRIS Program provides tracking information for of the chemicals for which assessments are either underway or to be initiated. Information on the status of these assessments can be found at the IRIS website at https://cfpub.epa.gov/ncea/iris2/atoz.cfm. Table 4 below provides the status of the 19 List A chemicals which have ongoing or planned EPA assessments.

Table 4: List A Chemicals (19) with Ongoing EPA Assessments or Nominated for Assessment

Chemical	**MCLG (mg/L)**	**Status**
Alpha/photon emitters	0 pCi/L	EPA/ORIA is conducting a review of alpha photon emitters
Arsenic, inorganic	0	The EPA IRIS Program is assessing inorganic arsenic. The assessment status can be found at: (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=278&forceAssessmentTab=true)
Atrazine	0.003	EPA is assessing atrazine and simazine under the pesticide registration review process.
Benzo(a)pyrene	0	The EPA IRIS Program is assessing benzo(a)pyrene. The assessment status can be found at: (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=136&forceAssessmentTab=true)
Beta/photon emitters	0 millirems per year	EPA is conducting a review of alpha and beta photo emitters.
Cadmium*	0.005	Cadmium is included in the EPA IRIS Multi-Year Agenda. (U.S. EPA, 2015).
Chromium (VI) as part of total Cr)	0.1	The EPA IRIS Program is assessing chromium VI. The assessment status can be found at: (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=144&forceAssessmentTab=true)
Di(2-ethylhexyl) phthalate (DEHP)*	0	Di(2-ethylhexyl) phthalate is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015)
Ethylbenzene	0.7	The EPA IRIS Program is assessing ethylbenzene. The assessment status can be found at: (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=51&forceAssessmentTab=true)
Glyphosate	0.7	EPA is assessing glyphosate under the pesticide registration review process
Mercury*	0.002	Mercury is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015).

Chemical	**MCLG (mg/L)**	**Status**
Nitrate (N)*	10	Nitrate is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015)
Nitrite (N)*	1	Nitrite is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015).
o-Dichlorobenzene (1,2-Dichlorobenzene)*	0.6	1,2-Dichlorobenzene is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015).
p-Dichlorobenzene (1,4-Dichlorobenzene)*	0.075	1,4-Dichlorobenzene is included in the EPA IRIS Multi-Year Agenda (U.S. EPA, 2015).
PCBs	0	The EPA IRIS Program is assessing PCBs. The assessment status can be found at: (https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=294&forceAssessmentTab=true)
Radium (226, 228)	0 pCi/L	EPA/ORIA is conducting a review of radium.

* Nominated in the IRIS Multi-Year Agenda (U.S.EPA, 2015)

4.2 Findings for List B Chemicals (42)

Based on the approach described in Sections 3.2 and 3.3 for List B chemicals, U.S. EPA evaluated the remaining 42 contaminants to determine if there were more recent RfDs and/or cancer risk assessments or any peer reviewed literature available that might support a change to the MCLG.

The tables presented in the Appendix B at the end of this document provide new assessment information on these List B chemicals. Two types of tables are available: one summarizing EPA assessments and the other summarizing assessments from other organizations.

- For each chemical, a table was constructed that presents a "Summary of the EPA Assessments" providing the basis for the current National Primary Drinking Water Regulations, including RfDs and cancer groups on which the MCLGs are based, and assessments by IRIS, OPP and/or OW (for fluoride only) that postdate the date for the regulation. The information in these tables provides the basis for the RfDs, including the critical effect, citation for the principal study, point of departure (whether it is a NOAEL, LOAEL, or BMDL), and breakdown of uncertainty factors. For OPP assessments, the Food Quality Protection Act (FQPA)[4] factor is also provided, when relevant. In addition, for cancer assessments, the year of the guidelines followed is presented, since the approach varied with the year of the guidelines. For a number of the chemicals evaluated between 1996 and 2001, the individual assessments provided the assessments under both the 1986 and 1996 guidelines. In such cases, only the

[4] The FQPA mandated consideration of an additional uncertainty factor to ensure protection of children for pesticide safety evaluations.

assessment under the 1996 guidelines is provided in the tables in the IRIS and OPP columns. All supporting U.S. EPA documents are listed in the reference section.

- Assessments by other organizations and completed within the scope of this review (August 2008 - December 2015) are also presented in the appendix. Where possible, non-cancer PODs initially expressed as water concentrations were converted to a reference dose as mg/kg/day, so that all values could be directly comparable. The citation to WHO refers to their Drinking Water Guidelines, and if another organization within WHO (JECFA, JMPR, CICAD, EHC) has a different value than WHO, it is noted.

If a new assessment is available and has been selected as the basis for a potential change in the MCLG, the information has been bolded in the table and the basis of the calculation for the potential new MCLG is provided in a footnote.

Although the date of "verification" is well-documented for the IRIS assessments, numerous additional revisions to the IRIS summary may be documented in the "Revision History" for each chemical, and the "last revised" date can be several years after the verification date, particularly for chemicals verified prior to 1996. The dates presented in Tables 1a through 42b for IRIS assessments refer to the verification date, as subsequent revision dates usually reflect minor editorial changes to the IRIS file. Risk assessments conducted by IRIS can be found at http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList and those by OPP can be found at http://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1.

Additional information on the quantitative portion of the cancer assessments is presented in these tables for the List B chemicals that have quantitative cancer slope factor assessments. The table shows both the quantitative assessment, the methods used for modeling the data and the process for extrapolating from the animal data to humans.

4.2.1 Findings for Consideration of a Change to the MCLG

Of the 42 List B chemicals evaluated, EPA found new information supporting potential changes to the MCLGs for 22 chemicals; for 18 chemicals this information was from EPA assessments. For four chemicals (methoxychlor, selenium, styrene, and 1,2,4-trichlorobenzene), an assessment by ATSDR, Health Canada, or CalEPA was selected as the source document suggesting that a change to the MCLGs could be considered. The information has been bolded in the table and the basis of the calculation for the possible new MCLG is provided in a footnote. Table 5 below provides the potential new MCLGs for the 22 chemicals along with the original MCLG, whether the MCLG could change, and the assessment that is the basis for the potential change. Because the MCLG for a carcinogen with a linear mode of action 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. For twelve (12) of the 22 chemicals there is potential for the MCLG to decrease.

Table 5: List B Chemicals with New Data and Potential New MCLG

Chemical	Original MCLG	New Noncancer Data[a]/Possible Impact on MCLG	New Cancer Data[a]/Possible Impact on MCLG	Potential New MCLG[b], Relevant New Assessment
Alachlor[c]	0 mg/L	Yes/Yes	No/No	0.04 mg/L, EPA OPP 2006a
Barium[c]	2 mg/L	Yes/Yes	No/No	6 mg/L, EPA IRIS 2005b
Beryllium[c]	0.004 mg/L	Yes/Yes	No/No	0.01 mg/L, EPA IRIS 1998c
Carbofuran[d]	0.04 mg/L	Yes/Yes	No/No	0.0006 mg/L, EPA OPP 2008a
Cyanide	0.2 mg/L	Yes/Yes	No/No	0.004 mg/L, EPA IRIS 2010c
1,1-Dichloroethylene[c]	0.007 mg/L	Yes/Yes	No/No	0.4 mg/L, EPA IRIS 2002d
cis-1,2-Dichloroethylene	0.07 mg/L	Yes/Yes	No/No	0.01 mg/L, EPA IRIS 2010b
2,4 Dichlorophenoxy-acetic Acid	0.07 mg/L	Yes/Yes	Yes/No	2 mg/L, EPA OPP 2013
Diquat[c]	0.02 mg/L	Yes/Yes	No/No	0.04 mg/L, EPA OPP TRED 2002e
Endothal[c]	0.1 mg/L	Yes/Yes	No/No	0.05 mg/L, EPA OPP 2005d
Fluoride	4.0 mg/L	Yes/Yes	No/No	0.9-1.2 mg/L EPA 2010a
Hexachlorocyclo-pentadiene[c]	0.05 mg/L	Yes/Yes	No/No	0.04 mg/L, EPA IRIS 2001a
Lindane	0.0002 mg/L	Yes/Yes	No/No	0.03 mg/L, EPA OPP 2002f
Methoxychlor	0.04 mg/L	Yes /Yes	No/No	0.0001 mg/L, CalEPA 2010a
Oxamyl[d]	0.2 mg/L	Yes/Yes	No/No	0.01 mg/L (children), EPA OPP 2010e
Picloram[c]	0.5 mg/L	Yes/Yes	No/No	1 mg/L, EPA OPP 1995b
Selenium	0.05 mg/L	Yes/Yes	No/No	0.04 mg/L, Health Canada 2014a
Styrene	0.1 mg/L	Yes/Yes	Yes/Yes	0 mg/L, CalEPA 2010c
Toluene[c]	1 mg/L	Yes/Yes	No/No	0.6 mg/L, EPA IRIS 2005c
1,1,1-Trichloroethane[c]	0.2 mg/L	Yes/Yes	No/No	14 mg/L, EPA IRIS 2007f

Chemical	Original MCLG	New Noncancer Data[a]/Possible Impact on MCLG	New Cancer Data[a]/Possible Impact on MCLG	Potential New MCLG[b], Relevant New Assessment
1,2,4-Trichlorobenzene	0.07 mg/L	Yes/Yes	Yes/No	0.7 mg/L, ATSDR 2010c
Xylenes[c]	10 mg/L	Yes/Yes	No/No	1 mg/L, EPA IRIS 2003d

[a]This column addresses whether there are new data from an updated EPA or non-EPA assessment since the latest OW assessment that was used to support the NPDWR.

[b] 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.

[c]A potential new MCLG was evaluated during the previous Six-Year review cycles.

[d] Updated exposure factors for children were used to estimate the potential MCLG for carbofuran and oxamyl. The potential new MCLGs were based on 10 kg body weight and 1L water consumption. An alternate MCLG for children from birth to less than 12 months was also calculated based on normalized drinking water intakes per unit body weight of 0.15L/Kg. This was determined based on the 90th percentile of drinking water consumption and the mean body weight for age groups, birth to <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months.

For ten of the chemicals on Table 5, the information identified in the most recent health based risk assessment demonstrates that the current MCLG is health protective because the new information suggests a potentially higher value. For the remaining 12, the most recent risk assessments identify a potentially lower MCLG assuming that there would be no change in the RSC utilized in the derivation of the original MCLG. For two of those cases, hexachlorocyclopentadiene and selenium, the difference between the current MCLG of 0.05 mg/L and a potential revised MCLG of 0.04 mg/L would not improve the level of public health protection given the UF applied in the derivation of the original and revised RfDs. In both cases the critical study has not changed, the RfD differs because of changes in risk assessment methodologies.

In the remaining cases (carbofuran, cyanide, cis dichloroethylene, endothal, fluoride, methoxychlor, oxamyl, styrene, toluene and xylene), the data on health effects suggests a potential to improve public health protection through a revision to the MCLG. However, as explained above occurrence at public drinking water systems and analytical method Minimum Reporting Levels (MRLs) must be considered when making the final determination as to whether there is a meaningful opportunity to improve public heath through revisions to the current rule. Additional information on fluoride health effects is provided in Appendix C.

4.2.2 Findings for No Consideration of a Change to the MCLG

No potential change to the MCLG is indicated for the remaining 20 List B chemicals listed in Table 6 below. For these 20 chemicals, there was no new assessment supporting an update to the MCLGs, and the literature search did not find new data that would likely affect the MCLG.

Table 6: Chemicals with No Potential Change to the MCLG

Chemical	Original MCLG (mg/L)	New Noncancer Data/Possible Impact on MCLG	New Cancer Data/Possible Impact on MCLG	New Data Source
Antimony	0.006	No/No	No/No	NA
Asbestos	7 million fibers/L	Yes/No	Yes/No	EPA IRIS 2014a
Chlordane	0	No/No	No/No	NA
Chlorobenzene	0.1	No/No	No/No	NA
Dalapon	0.2	No/No	No/No	NA
1,2-dibromo-3-chloroporpane (DBCP)	0	No/No	No/No	NA
trans-1,2-Dichloroethylene	0.1	Yes/No	No/No	EPA IRIS 2010b
Di(2-ethylhexyl) adipate (DEHA)	0.4	No/No	No/No	NA
Dinoseb	0.007	No/No	No/No	NA
Dioxin	0	Yes/No	No/No	EPA IRIS 2012b

Endrin	0.002	No/No	No/No	NA
Ethylene dibromide	0	No/No	No/No	NA
Heptachlor	0	No/No	No/No	NA
Heptachlor epoxide	0	No/No	No/No	NA
Hexachlorobenzene	0	No/No	Yes/No	EPA OPP 2008b
Pentachlorophenol	0	Yes/No	Yes/No	EPA IRIS 2010
Thallium	0.0005	Yes/No	No/No	EPA IRIS 2009a
Toxaphene	0	No/No	No/No	NA
2,4,5-TP (Silvex)	0.05	No/No	No/No	NA
1,1,2-Trichloroethane	0.003	No/No	No/No	NA

A new U.S. EPA assessment, including a new RfD, was available for pentachlorophenol and dioxin which are carcinogens. Because the MCLG is zero for carcinogens (categories A, B1, or B2 under the 1986 guidelines; "carcinogenic to humans" or "likely to be carcinogenic to humans" under the 2005 guidelines), changes to the RfD will not affect the MCLG. Therefore, no change to the MCLG is suggested for these particular chemicals. For *trans*-1,2-dichloroethylenethe the update to the original IRIS assessment did not result in a change in the RfD that was used for MCLG derivation. For thallium, the IRIS update recommended by Six-Year Review 1 was unable derive an RfD because of technical deficiencies in the reporting of the original critical study and lack of better data from any of the more recent publications. The thallium MCL is based on the analytical method PQL and therefore remains protective.

5. SUMMARY

The 1996 amendments to the Safe Drinking Water Act (SDWA) require the United States Environmental Protection Agency (EPA) to review every six years existing NPDWRs and determine which, if any, are candidates for revision. Under the Six-Year Review 3, the Office of Water of U.S. EPA has completed a review of 76 water contaminants currently regulated under the SDWA. EPA identified 12 NPDWRs ongoing, or pending regulatory actions deferred them from a detailed health effects review at this time. Of the remaining contaminants, 19 List A chemicals are the subject of ongoing U.S. EPA assessments or are nominated for health assessment, thus the revision to these MCLGs is not appropriate at this time.

This assessment focused therefore on the evaluation of the 42 List B chemicals to determine whether new information is available that could affect the MCLGs and perhaps the MCLs. Assessments prepared by a wide range of authoritative bodies, and the published literature was searched for new data on general toxicity, reproductive/developmental toxicity, and carcinogenicity.

Based on this assessment, U.S. EPA identified 22 List B chemicals that had changes to their EPA OPP or IRIS health assessments or had relevant new assessments by Health Canada, CalEPA, or ATSDR that could potentially change the MCLGs. For the remaining 20 List B chemicals, the Agency concluded that based on the analysis of the current information, no change to the MCLG is indicated at this time. For twelve (12) of the 22 chemicals (in bold below) there is potential for the MCLG to decrease. The 22 chemicals are listed below:

Alachlor	**Hexachlorocyclopentadiene**
Barium	Lindane
Beryllium	**Methoxychlor**
Carbofuran	**Oxamyl (vydate)**
Cyanide, free	Picloram
2,4-D (2,4-Dichlorophenoxy Acetic Acid)	**Selenium**
1,1-Dichloroethylene	**Styrene**
***cis*-1,2-Dichloroethylene**	**Toluene**
Diquat	1,2,4-Trichlorobenzene
Endothall	1,1,1-Trichloroethane
Fluoride	**Xylenes**

Note the chemicals above were identified based on health effects only and independent of other considerations (e.g., analytical and occurrence data) that may influence the final selection of contaminants recommended for revision. For additional information on other considerations in determining if a revision is appropriate at this time, see the following support documents:

- *Analytical Feasibility Support Document for the Third Six-Year Review of National Primary Drinking Water Regulations: Chemical Phase Rules and Radionuclides Rules* (U.S. EPA, 2016a),
- *Development of Estimated Quantitation Levels for the Third Six-Year Review of National Primary Drinking Water Regulations (Chemical Phase Rules)* (U.S. EPA, 2016b),
- *Occurrence Analysis for Potential Source Waters for the Third Six-Year Review of National Primary Drinking Water Regulations* (U.S. EPA, 2016c), and
- *The Analysis of Regulated Contaminant Occurrence Data from Public Water Systems in Support of the Third Six-Year Review of National Primary Drinking Water Regulations: Chemical Phase Rules and Radionuclides Rules* (U.S. EPA, 2016i).

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[5] The 2010 ATSDR draft Toxicological Profile for toxaphene has been superseded by a revised 2014 Toxicological Profile; however, the url has not changed. Thus, clicking on the url provided for ATSDR, 2010 will open the 2014 Toxicological Profile. The 2010 draft Toxicological Profile is no longer available.

[6] The 2010 ATSDR draft Toxicological Profile for 1,2,4-trichlorobenzene has been superseded by a revised 2014 Toxicological Profile; however, the url has not changed. Thus, clicking on the url provided for ATSDR, 2010 will open the 2014 Toxicological Profile. The 2010 draft Toxicological Profile is no longer available.

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APPENDIX A –LIST A TOXICITY TABLES FOR SELECTED CHEMICALS INCLUDED IN IRIS MULTI-YEAR AGENDA

For eight List A chemicals (cadmium, 1,2-dichlorobenzene, 1,4-dichlorobenzene, nitrate, nitrite, mercury, DEHP and uranium), an initial literature search was conducted and a preliminary evaluation of the literature was completed. Subsequent to these literature searches the IRIS Multi-Year Agenda was published (U.S. EPA, 2015). The IRIS Program maintains an agenda of chemicals for which assessments are either underway or to be initiated. The IRIS Program recently published the IRIS Multi-Year Agenda that lists a total of 37 chemicals (U.S. EPA, 2015). In this plan the chemicals on the IRIS 2012 agenda were re-prioritized to determine which assessments should be initiated in the next few years. In addition, some chemicals that were not part of the 2012 agenda were identified and included in this re-prioritization. The top priority chemical assessments are those with the highest potential public health impacts and/or exposure and would be useful in anticipated EPA decision-making.

Tables 1a through 8b in this appendix provide toxicity information on the 8 List A chemicals that are included in the IRIS agenda (U.S. EPA, 2015). EPA reviewed available health assessments from 2008 (one year before the Six-Year Review 2 was finalized) through December 2015. EPA also conducted literature search from 2008 (one year before the Six-Year Review 2 was finalized) to December 2014.

Tables with numbers ending with letter “a” provide summary of EPA Assessments. Tables with numbers ending with letter “b” provide summary of relevant non-EPA Assessments. For each chemical table numbers ending with letter “a” provides the basis for the current National Primary Drinking Water Regulations, including RfDs and cancer groups on which the MCLGs are based, and assessments by IRIS, and OPP that postdate the date for the regulation (through December 2015). These tables provide information on RfDs, including the critical effect, citation for the principal study, point of departure (whether it is a NOAEL, LOAEL, or BMDL), and breakdown of uncertainty factors from EPA assessments. In addition, for cancer assessments, the year of the guidelines followed is presented, since the approach varied with the year of the guidelines. For a number of the chemicals evaluated between 1996 and 2001, the assessment document provided the assessments under both the 1986 and 1996 guidelines. In such cases, only the assessment under the 1996 guidelines is provided in the tables in the IRIS and OPP columns. Additional information on the quantitative portion of the cancer assessments is presented in these tables for chemicals for which quantitative assessments are available. The table shows both the quantitative assessment and the methods used for modeling the data and for extrapolation from the animal data.

Assessments by other organizations which were completed within the scope of this review (August 2008- December 2015) for List A nominated chemicals for health assessment are presented in tables with numbers ending with letter “b”. The citation to WHO refers to their Drinking Water Guidelines, and if another organization within WHO (JECFA, JMPR, CICAD, EHC) has a different value than WHO, it is noted.

All the U.S. EPA documents and references for the non-EPA assessments are listed in the reference section.

Table 1a. Summary of EPA Assessments: Cadmium CASRN 7440-43-9

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Cadmium (1991g)	0.005	0.005	0.0005/ 0.005 (LOAEL)/ 10 (1H, 10L) estimated LOAEL in human study/ Renal dysfunction/ Friberg et al., 1974	D, Not classifiable as to human carcinogenicity by the oral route of exposure (1986i guidelines)	0.18 25%[7]	Water[8]: 0.0005 (1988d) / 0.005 (NOAEL)/ 10 (10H)/ Significant proteinuria/ Food: 0.001 (1988d)/ 0.01 (NOAEL)/ 10 (10H)/ Significant proteinuria/ 1985c	B1, Probable human carcinogen; No quantitative assessment for the oral route (1986i guidelines; 1986b)[9]	--	--

[7] This departure from the default RSC of 20% was based on evidence of greater bioavailability from water in comparison with food (54 FR 22062).
[8] Since the fraction of ingested Cd that is absorbed appears to vary with the source (e.g., food vs. drinking water), different % absorption was used for food and water in the toxicokinetic model used to extrapolate from concentration in the kidney to intake in food or water; i.e. 2.5% absorption of cadmium from food and 5% absorption of the total cadmium dose from water. The model also assumes that 0.01% of the total body burden of cadmium is excreted per day.
[9] Based on the revised "Group B1" cancer classification, under the EPA 1986i cancer classification system, the MCLG for cadmium could be potentially revised to zero, however, the Agency believes that an updated assessment is needed based on the most current 2005a U.S. EPA cancer classification guidelines.

Table 1b. Summary of Assessments by Other Organizations: Cadmium CASRN 7440-43-9

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL (mg/kg/day) (year)/ Point of Departure / UF (breakdown of UFs)/ Effect/ Citation	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Cadmium	0.0001 (chronic MRL) (2012)/ 0.00033 mg/kg/day ($UCDL_{10}$)[10] / UF of 3 (UFH of 3)[11]	--	--	0.003 mg/L provisional tolerable weekly intake (2011a, WHO)	--	--	--	--	Group 1, Carcinogenic to humans (2012e)	Known to be a human carcinogen (2014)

Note: ATSDR assessment for cadmium only provided quantification of noncancer effects, and there is a need for a cancer dose response assessment. From the primary literature review EPA found several studies reporting both cancer and noncancer effects (e.g., neurodevelopmental outcomes, cardiovascular effects), and at the minimum these studies need to be further evaluated (Ciesielski et al. 2012, Larsson et al., 2015a, Larsson et al., 2015b, Nawrot et al., 2015; Tellez-Plaza et al., 2012, Åkesson et al 2014).

[10] $UCDL_{10}$ is the 95% lower confidence limit on the estimated internal cadmium dose (urinary cadmium expressed as ug/g creatinine) corresponding to the probability of 10% excess risk of low molecular weight proteinuria.

[11] Using the MRL of 0.00011 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 25% RSC, an MCLG of 0.001 mg/kg/day is derived.

Table 2a. Summary of EPA Assessments: 1,2-Dichlorobenzene (o-Dichlorobenzene) CASRN 95-50-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,2-Dichlorobenzene (o-Dichlorobenzene) (1991g)	0.6	0.6	0.09/ 85.7 (NOAEL)/ 1000 (10H, 10A, 10D)/ No treatment-related adverse effects noted; renal tubular regeneration noted but not interpreted as dose-related/ NTP, 1985	D, Not classifiable as to human carcinogenicity (1986i guidelines)	3 20%	0.09 (1989a) 85.7 (NOAEL)/ 1000 (10H, 10A, 10D), No treatment-related adverse effects noted; renal tubular regeneration noted but not interpreted as dose-related/ NTP, 1985	D, Not classifiable as to human carcinogenicity (1986i guidelines; 1989a)	--	--

Table 3a. Summary of EPA Assessments: 1,4-Dichlorobenzene (p-Dichlorobenzene) CASRN 106-46-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,4-Dichlorobenzene (p-Dichlorobenzene) (1987i)	0.075	0.075	0.1/ 150 (adjusted: 107 mg/kg/day) (NOAEL)/ 1000 (10H, 10A, 10S)/ Renal cortical degeneration in male rats/ Battelle 1980; NTP, 1987	C, Possible human carcinogen (1986i guidelines)/ From rat study[12]: Potency: 2×10^{-2} per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 1.8×10^{-2} mg/L/(BW)2/3/ Linearized multistage model	3.75 20% (and a factor of 10 for class C, possible carcinogen-icity)	Not finalized	--	0.025 (2008c)/ 25 (NOAEL)/ 100 (10H, 10A)/ increased liver weight in males and increased alkaline phosphatase and liver weight, irritation to GI tract in females/ Harrington and Thake, 1995	Not Likely to be Carcinogenic to Humans below doses that do not perturb normal liver homeostasis (2005a guidelines) (2008c)

[12] Six Year Review 2 Report also provides the following data from a mouse study: Potency: 6E-3 per mg/kg-day; Drinking water concentration at 10-5 risk level: 5.8E-2 mg/L.

Table 3b. Summary of Assessments by Other Organizations: 1,4-Dichlorobenzene (p-Dichlorobenzene) CASRN 106-46-7

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year) mg/kg/day (year)	Cancer classification (year)			
1,4-Dichlorobenzene (p-Dichlorobenzene)	--	--	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

Table 4a. Summary of EPA Assessments: Di(2-ethylhexyl) phthalate (DEHP) CASRN 117-81-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Di(2-ethylhexyl) phthalate (DEHP) (1991d)	0	0.006 (PQL)	0.02/ 19 (LOAEL)/ 1000 (10H,10A, 10L/S for less than chronic study and LOAEL)/ Increase in relative liver weights/ Carpenter et al., 1953	B2, Probable human carcinogen (1986i guidelines)/ Potency: 0.014 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-2} mg/L/ (BW)2/3/ Linearized multistage model	0.7 --	0.02 (1986c) / 19 (LOAEL)/ 1000 (10H,10A, 10L/S for less than chronic study and LOAEL)/ Increase in relative liver weights/ Carpenter et al., 1953	B2, probable human carcinogen (1986i guidelines; 1987d)/ Potency: 0.014 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-2} mg/L/ (BW)2/3/ Linearized multistage model	--	--

Note: For di(2-ethylhexyl) phthalate, EPA identified new assessments on cancer classifications (ACGIH, 2010, IARC, 2012f, NIEHS 2014, ECB, 2008). Further, the Six-Year Review 3 literature search identified a new study (Lin et al., 2011) that reported impaired glucose homeostasis at 1.25 mg/kg/day upon in utero and postnatal exposures.

Table 4b. Summary of Assessments by Other Organizations: Di(2-ethylhexyl) phthalate (DEHP) CASRN 117-81-7

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Di(2-ethylhexyl) phthalate (DEHP)	--	--	--	--	--	--	--	--	Group 2B, Possibly carcinogenic to humans (2012f)	Reasonably anticipated to be a human carcinogen (2014)

Table 5a. Summary of EPA Assessments: Mercury (Inorganic) CASRN 7439-97-6

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Mercury (Inorganic) (1991g)	0.002	0.002	0.0003[13]/ 1000 (Not specified)/ Mercuric chloride-induced autoimmune glomerulonephritis/ 1987j; Druet et al., 1978; Bernaudin et al., 1981; Andres 1984	--	0.01 20%	0.0003 (1988i)/ 0.317 (LOAEL)/ 1000 (10A,H, 10L, 10S)/ Mercuric chloride-induced autoimmune glomerulonephritis/ 1987j; Druet et al., 1978; Bernaudin et al., 1981; Andres, 1984	Mercuric chloride: C, Possible human carcinogen by 1986i guidelines; 1994a Elemental Mercury: D, Not classifiable as to human carcinogenicity by 1986i guidelines (1994b, EPA/IRIS) Methylmercury: C, Possible human carcinogen by 1986i guidelines; 1994d	--	--

[13] The RfD for mercury was back-calculated from the DWEL using 2 L water consumption and 70 kg body weight in the following equation (0.01 mg/L × 2 L) / 70 kg = 0.00029 mg/kg-day, rounded to 0.0003 mg/kg-day.

Table 6a. Summary of EPA Assessments: Nitrate (as N) CASRN 14797-55-8

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Nitrate (as N) (1991g)	10	10	1.6 nitrate-nitrogen/ 1.6 (10 mg/L) (NOAEL)/ 1/ Methemoglobinemia in infants/ Bosch et al., 1950; Walton, 1951	--	10[14] --	1.6 nitrate-nitrogen/ (1990c)/ 1.6 (10 mg/L) (NOAEL)/ 1/ Methemoglobinemia in infants/ Bosch et al., 1950; Walton, 1951	--	--	--

[14] Nitrate assessment is based on the concentration in the drinking water for an exposed human population.

Table 6b. Summary of Assessments by Other Organizations: Nitrate (as N) CASRN 14797-55-8

Chemical	ATSDR	CalEPA		WHO[15] Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Nitrate (as N)	--		--	50 mg/L[16] (2011b, WHO)	--	Nitrate: 45; equivalent to 10 mg/L MAC nitrate-nitrogen (2013)[17]			--	--

[15] WHO refers to Drinking Water Guidelines, unless otherwise specified. If another organization within WHO (JECFA, JMPR, CICAD, EHC) has a different value than WHO, it is included as a separate line. If another organization reports the same value as the WHO, it is indicated by footnote.
[16] Guideline value is presented as mg/L only.
[17] The noncancer value is presented as mg/L only. The value is derived by dividing the NOAEL which is a concentration in drinking water for humans by the uncertainty factor.

Table 7a. Summary of EPA Assessments: Nitrite (as N) CASRN 14797-65-0

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Nitrite (as N) (1991g)	1	1	0.16 nitrite- nitrogen/ Nitrate RfD of 1.6 nitrate-nitrogen[18]/ 1 (MF = 10)/ Methemoglobinemia in infants/ Bosch et al., 1950; Walton, 1951	--	1 --	0.1 nitrite-nitrogen (1986l)/ 1[19] (10 mg/L nitrate-nitrogen) (NOAEL)/ 1 (MF = 10)/ Methemoglobinemia in infants/ Walton, 1951	--	--	--

[18] Extrapolated from nitrate RfD of 1.6 mg/kg-day, assuming 10% of nitrate converted to nitrite. Assumes a 4 kg child ingesting 0.64 L/day.
[19] 10 mg/L converted to 1.0 mg/kg-day assuming 10 kg child ingesting 1 L/day.

Table 7b. Summary of Assessments by Other Organizations: Nitrite (as N) CASRN 14797-65-0

Chemical	ATSDR	CalEPA		WHO[20] Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Nitrite (as N)	--		--	3 mg/L[21] (2011b, WHO)	--	3; equivalent to 1 mg/L measured (2013)[22]			--	--

[20] WHO refers to Drinking Water Guidelines, unless otherwise specified. If another organization within WHO (JECFA, JMPR, CICAD, EHC) has a different value than WHO, it is included as a separate line. If another organization reports the same value as the WHO, it is indicated by footnote.
[21] Guideline value is presented as mg/L only.
[22] The noncancer value is presented as mg/L only. The value is derived by dividing the NOAEL which is a concentration in drinking water for humans by the uncertainty factor.

Table 8a. Summary of EPA Assessments: Uranium CASRN 7440-61-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Uranium (2000c)	0	0.03[23] (feasibility and cost-benefit analysis)	0.0006 µg/kg/day/ 0.06 (LOAEL)/ 100 (10H, 3A, 3L) (minimum LOAEL)/ Renal toxicity/ Gilman et al., 1998	A, Known human carcinogen; No quantitative assessment (1986i guidelines)[24]	20 µg/L 100%	0.003 (1989e)[25]/ 2.8 (LOAEL)/ 1000 (10H, 10A, 10S) Initial body weight loss; moderate nephrotoxicity/ Maynard and Hodge, 1949	--	--	--

[23] EPA ORIA is the principal health assessor for radionuclides. The 2000 radionuclides rule was a collaboration between EPA OW and ORIA. See 40 CFR 141.
[24] The Office of Water Criteria Document (U.S. EPA, 1991f) has derived risk specific concentration for a cancer risk of 1×10^{-4} for lifetime consumption of various isotopes of uranium using the RADRISK program. For example, for combined U234 and U238 a concentration of 120 pCi/L is associated with a 1×10^{-4} cancer risk.
[25] The IRIS RfD for natural uranium has been withdrawn. The Uranium entry in the Table is for Uranium, soluble salts.

Table 8b. Summary of Assessments by Other Organizations: Uranium CASRN 7440-61-1

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Uranium	0.0002 intermediate MRL (2013)	--	--	0.06 provisional (2012, WHO)	--	--	--	--	IARC 2012a	--

Note: For uranium, a number of peer reviewed studies were identified since Six-Year Review 2. The new data on the noncancer health effects of soluble uranium from oral exposure include bone effects and kidney damage is considered in the NPDWR.

APPENDIX B - LIST B TOXICITY TABLES FOR CHEMICALS THAT ARE EVALUATED FOR POTENTIAL IMPACT ON THE MCLG

Tables 1a through 42b in this appendix provide key information on the 42 List B chemicals evaluated in this assessment. EPA reviewed available health assessments from 2008 (one year before the Six Year Review 2 was finalized) through December 2015. EPA also conducted literature search from 2008 (one year before the Six Year Review 2 was finalized) to December 2014. Tables with numbers ending with letter "a" provide summary of EPA Assessments. Tables with numbers ending with letter "b" provide summary of relevant non-EPA Assessments. For each chemical table numbers ending with letter "a" provides the basis for the current National Primary Drinking Water Regulations, including RfDs and cancer groups on which the MCLGs are based, and assessments by IRIS, EPA OPP and/or OW (fluoride only) that postdate the date for the regulation. These tables are numbered 1a through 42b and provide the basis for the RfDs, including the critical effect, citation for the principal study, point of departure (whether it is a NOAEL, LOAEL, or BMDL), and breakdown of uncertainty factors. For EPA OPP assessments, the Food Quality Protection Act (FQPA)[26] factor is also provided, when relevant. In addition, for cancer assessments, the year of the guidelines followed is presented, since the approach varied with the year of the guidelines. For a number of the chemicals evaluated between 1996 and 2001, the assessment document provided the assessments under both the 1986 and 1996 guidelines. In such cases, only the assessment under the 1996 guidelines is provided in the tables in the IRIS and OPP columns. All supporting U.S. EPA documents are listed in the reference section. Additional information on the quantitative portion of the cancer assessments is presented in these tables for chemicals for which quantitative assessments are available. The table shows both the quantitative assessment and the methods used for modeling the data and for extrapolation from the animal data. If an IRIS or EPA OPP or OW assessment is the Relevant New Assessment on which to base a potential change to the MCLG, the information has been bolded in the table and the basis of the calculation for the potential new MCLG is provided in a footnote.

Assessments by other organizations which were completed within the scope of this review (August 2008- December 2015) for List B chemicals are also presented in tables with numbers ending with letter "b". Where possible, non-cancer PODs initially expressed as water concentrations were converted to the reference value in dose as mg/kg/day, so that all values could be directly comparable at a glance. The citation to WHO refers to their Drinking Water Guidelines, and if another organization within WHO (JECFA, JMPR, CICAD, EHC) has a different value than WHO, it is noted.

[26] The FQPA mandated consideration of an additional uncertainty factor to ensure protection of children for pesticide safety evaluations.

Table 1a. Summary of EPA Assessments: Alachlor CASRN 15972-60-8

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Alachlor (1991g)	0	0.002 (PQL)[33]	0.01/ 1 mg/kg/day (NOAEL)/ 100 (10H, 10A)/ Hemosiderosis, hemolytic anemia/ Naylor et al., 1984	B2, Probable human carcinogen (1986i guidelines)	0.35 µg/L --	0.01 (1991b)/ 1 mg/kg/day (NOAEL)/ 100 (10H, 10A)/ Hemosiderosis, hemolytic anemia/ Monsanto, 1984	--	**0.005 (2006a, 2007e)** [34]**/ 0.5 mg/kg/day (NOAEL) / 100 (10H, 10A)/ nonlinear cancer assessment/ nasal tumors**	Likely to be a human carcinogen at high doses; not likely to be a human carcinogen at low doses (2005a guidelines; 2006a)/ 0.005 mg/kg/day/ Nonlinear MOA

[33] The current MCL is based on a PQL of 0.002 mg/L, neither analytical nor treatment feasibility would be a limiting factor for a possible higher level of 0.04 mg/L for the MCLG.

[34] The data indicate that alachlor's tumorigenicity is operating by a nonlinear mode of action. OPP (U.S. EPA, 1998d, 2001b, 2006a) concluded that alachlor causes nasal turbinate tumors via the generation of a reactive metabolite that leads to cytotoxicity and regenerative proliferation in the nasal epithelium; sustained cytotoxicity and proliferation is needed to lead to neoplasia. Based on this MOA assessment a non-linear dose response assessment is appropriate. Therefore, using the POD of 0.5 mg/kg/day identified by OPP for this endpoint and the UF of 100 (10H, 10A) would result in a health reference value of 0.005 mg/kg/day. Assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a MCLG derived from this value is 0.035 mg/L (rounded to 0.04 mg/L). If determined appropriate to revise the new potential increased MCLG would be based on the nonlinear cancer assessment.

Table 2a. Summary of EPA Assessments: Antimony CASRN 7440-36-0

Chemical (Date of regulation)	**U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)**					**U.S. EPA IRIS**		**U.S. EPA OPP**	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Antimony (1992b)	0.006	0.006 (PQL)	0.0004/ 0.43 (LOAEL)/ 1000 (10H, 10A, 10L)/ decreased longevity, decreased blood glucose and increased blood cholesterol/ Schroeder et al., 1970	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.014 40%	0.0004 (1985a) / 0.35 (LOAEL)/ 1000 (10H, 10A, 10L)/ decreased longevity, blood glucose, and cholesterol/ Schroeder et al., 1970	--	--	--

Table 3a. Summary of EPA Assessments: Asbestos CASRN 1332-21-4

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & PSG	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Asbestos (1991g)	7 million fibers/L	7 million fibers/L	--	Not available via ingestion; A, Known human carcinogen (1986i guidelines) via inhalation/ Potency: 1.4×10^{-13} per fiber/L; Drinking water concentration at 10^{-5} risk level: 7.1×10^{7} fiber/L/ (B/W)2/3/ Linearized multistage model	--	------ (2014a) NCEA/IRIS)[35]	Not available via ingestion[36]; A, Known human carcinogen via inhalation (1986i guidelines; 1987b)[37,38] Libby amphibole asbestos is carcinogenic to humans via inhalation (2014a, NCEA/IRIS)	--	--

[35] An oral RfD was not derived because inhalation is the primary route of concern and oral data for Libby Amphibole asbestos is lacking (U.S. EPA, 2014a).
[36] The IRIS reassessment of the noncancer health risks resulting from exposure to asbestos (from Libby Montana) identified during the first six-year review (U.S. EPA, 2002b) was still in progress as an external review draft submitted to the Science Advisory Board (SAB) in 2012.EPA/IRIS (2014a) is cited in the table.
[37] The External Review Draft of the IRIS Toxicological Review for a mixture of amphibole fibers identified in the Rainy Creek complex and present in ore from the vermiculite mine near Libby, MT could not assess oral carcinogenicity (U.S. EPA, 2014a); however, Libby Amphibole asbestos is considered carcinogenic to humans by the inhalation route of exposure by 2005a EPA cancer guidelines.
[38] Oral carcinogenicity could not be assessed in the IRIS external review draft for a mixture of amphibole fibers (U.S. EPA, 2014a); however, Libby Amphibole asbestos is considered carcinogenic to humans by the inhalation route of exposure by 2005a EPA cancer guidelines.

Table 3b. Summary of Assessments by Other Organizations: Asbestos CASRN 1332-21-4

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Asbestos (1991g)	--	--	--	--	--	--	--	--	All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite): Group 1, Carcinogenic to humans (2012c)	Known to be a human carcinogen (2014)

Table 4a. Summary of EPA Assessments: Barium CASRN 7440-39-3

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Barium (1991g)	2	2	0.07/ 0.21 (adjusted NOAEL)/ 3 H/ No changes in blood pressure, or serum chemistry/ Wones et al., 1990	D, Not classifiable as to human carcinogenicity (1986i guidelines)	2 100%	**0.2 (2005b)[39]/ 63 (BMDL$_{05}$/ 300 (10H, 10A, 3D)/ Nephropathy/ NTP, 1994**	Not likely to be carcinogenic to humans following oral exposure (1996 guidelines; 1998a, b)	--	--

[39] Based on the 2005b IRIS RfD the MCLG could increase. The RfD is 0.2 mg/kg-day and assuming 70 kg body weight, 2 liters water intake per day, a DWEL of 7 mg/L can be derived. This value is three times the current value. 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, 2000b). 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. Using and 80% RSC, the potential new MCLG would be 6 mg/L.

Table 5a. Summary of EPA Assessments: Beryllium CASRN 7440-41-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Beryllium (1992b)	0.004	0.004	0.005/ 0.538 (NOAEL)/ 100 (10H, 10A)/ No effect/ Schroeder and Mitchener, 1975	B2, Probable human carcinogen (1986i guidelines)/ Potency: 4.3 per mg/kg/day Drinking water concentration at 10^{-5} risk level: 8×10^{-5} mg/L/(BW)2/3/ Linearized multistage model	0.2 20% Also factor of 10 for category II	**0.002 (1998c)[40]/ 0.46 (BMD_{10})/ 300 (10H, 10A, 3D)/ Ulcerative inflammatory lesions of small intestine/ Morgareidge et al., 1976**	Carcinogenic potential of ingested beryllium cannot be determined (1996 guidelines; 1998c)	--	--

[40] The MCLG could increase based on the 1998c IRIS. The RfD is 0.002 mg/kg-day and assuming 70 kg body weight and 2 liters water intake per day, the DWEL would be 0.05 mg/L. Using a 20% RSC, the potential new MCLG would be 0.01 mg/L.

Table 5b. Summary of Assessments by Other Organizations: Beryllium CASRN 7440-41-7

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Beryllium	--	--	--	--	--	--	--	--	Group 1, Carcinogenic to humans (2012d)	Known to be a human carcinogen (2014)

Table 6a. Summary of EPA Assessments: Carbofuran CASRN 1563-66-2

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Carbofuran (1991g)	0.04	0.04	0.005/ 0.5 (NOAEL)/ 100 (10H, 10A)/ Acetylcholinesterase inhibition and testicular degeneration/ FMC Corp., 1983	E, Evidence of noncarcinogenicity (1986i guidelines)	0.175 20%	0.005 (1987c)/ 0.5 (NOAEL)/ 100 (10H, 10A)/ RBC and plasma cholinesterase inhibition, and testicular and uterine effects/ FMC Corp., 1983	--	**0.0003(2008a)[41]/0.03 ($BMDL_{10}$)/ 100 (10H, 10A) Brain acetylcholinesterase inhibition in PND11male pups/ FMC Corp., 2005**	Not likely to be a human carcinogen (2005a guidelines; 2006a)

[41] OPP's value for carbofuran is an acute RfD for cholinesterase inhibition, which OPP has determined is protective of chronic exposures; the potential new MCLG is 0.0006 mg/L assuming a RfD of 0.0003 mg/kg-day assuming 10kg/1L (children) and an RSC of 20%. OPP has also derived an aPAD of 0.00006 mg/kg-day based on this RfD to protect infants and children from neurotoxic effects (FQPA 5x). A chronic RfD was not derived because of the rapid recovery of AChE activity and an acute exposure based RfD that is considered protective for chronic exposure. An alternate potential MCLG of 0.0004 mg/L can be derived for children from birth to less than 12 months at the 90th percentile of 0.15 L/kg (U.S. EPA, 2011a Exposure Factor Handbook, based on Table 3-19) as follows: 0.0003 mg/kg/day x 0.2 x 10kg/1.5L = 0.0004 mg/L.

Table 7a. Summary of EPA Assessments: Chlordane CASRN 12789-03-6 (IRIS), 57-74-9 (lit search)

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Chlordane (1991g)	0	0.002 (PQL)	0.00005/ 0.045 (LOAEL)/ 1000 (10H, 10A, 10L)/ Liver necrosis in male rats/ Yonemura et al., 1983	B2, Probable human carcinogen (1986i guidelines)/ Potency: 1.3 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 2.7×10^{-4} mg/L/(BW)2/3/ Linearized multistage model	--	0.0005 (1997)/ 0.15 (NOAEL)/ 300 (10H, 10A, 3D)/ Liver necrosis in mice/ Khasawinah and Grutsch, 1989; IRDC 1973; NCI 1977	Likely to be a carcinogen by all routes of exposure (1996 guidelines; 1997)/ Potency: 0.35 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 1×10^{-3} mg/L/(BW)3/4/ Linearized multistage model	--	--

Table 8a. Summary of EPA Assessments: Chlorobenzene (Monochlorobenzene) CASRN 108-90-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Chlorobenzene (Monochlorobenzene) (1991g)	0.1	0.1	0.02/ 19 (NOAEL)/ 1000 (10H, 10A, 10S)/ Histopathologic changes in the liver/ Monsanto Company, 1967; Knapp et al., 1971	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.7 20%	0.02 (1989b)/ 19 (NOAEL)/ 1000 (10H, 10A, 10S)/ Histopathologic changes in the liver/ Monsanto Company, 1967	D, Not classifiable as to human carcinogenicity (1986i guidelines; 1990a)	--	--

Table 8b. Summary of Assessments by Other Organizations: Chlorobenzene (Monochlorobenzene) CASRN 108-90-7

Chemical (List A or B)	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Chlorobenzene (Monochlorobenzene)	--	0.03 (2014)[42]	--	--	--	--	--	--	--	--

[42] The public health goal derived by CalEPA is based on noncancer effects. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 9a. Summary of EPA Assessments: Cyanide CASRN 57-12-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Cyanide (1992b)	0.2	0.2	0.02/ 10.8 (NOAEL)/ 100 (10H, 10A) (MF=5 for apparent tolerance via food compared to water)/ Absence of clinical and histological effects/ Howard and Hanzal 1955	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.7 20%	**0.00063 (2010c)[43]/1.9 ($BMDL_{1SD}$)/ 3000 (10H, 10A, 10S, 3D)/ decrease cauda epididymis weight/ NTP, 1993**	Inadequate information to assess the carcinogenic potential (2005a guidelines; 2010c)	0.004 (2006b)/ 0.4 (LOAEL)/ 100 (10H, 10S)/ Clinical signs including nausea, vomiting, headaches, dizziness	The classification of the carcinogenic potential could not be determined due to the absence of acceptable cancer studies in rats and mice (2005a guidelines; 2006b)

[43] Using the RfD of 0.00063 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.0044 mg/L (rounded to 0.004 mg/L).

Table 10a. Summary of EPA Assessments: 2,4-Dichlorophenoxyacetic Acid (2,4-D) CASRN 94-75-7

Chemical (Date of regulation)	**U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)**					**U.S. EPA IRIS**		**U.S. EPA OPP**	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
2,4-D (2,4-Dichlorophenoxyacetic Acid) (1991g)	0.07	0.07	0.01/ 1 (NOAEL)/ 100 (10H, 10A)/ Hematologic, hepatic and renal toxicity/ Serota et al., 1983	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.35 20%	0.01 (1983)/ 1 (NOAEL) / 100 (10H, 10A)/ Hematologic, 0.02 hepatic and renal toxicity/ Serota et al., 1983	--	**0.21 (2013)[44]/21 (NOAEL) 100 (10H, 10A)/ kidney toxicity**	D, Not classifiable as to human carcinogenicity (1986i guidelines)

[44] The MCLG could increase based on the RfD from 2013 OPP. The RfD is 21 mg/kg/day, assuming 70 kg body weight and 2 liters water intake per day, and a 20% RSC, the potential new MCLG would be 2 mg/L.: 0.21 mg/kg-day x 0.2 x 70kg/2L = 1.47 mg/L, which is rounded to 2 mg/L.

Table 10b. Summary of Assessments by Other Organizations: 2,4-Dichlorophenoxyacetic Acid (2,4-D) CASRN 94-75-7

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
2,4-D (2,4-Dichlorophenoxy acetic Acid)	--	0.005 (2009a)[45]	Due to lack of conclusive findings in the epidemiological data, and the lack of evidence in animal studies for carcinogenicity, carcinogenicity is not used as the endpoint for the PHG (2009a)	--	--	--	--	--	--	--

[45] The public health goal derived by CalEPA is based on noncancer effects. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 11a. Summary of EPA Assessments: Dalapon (2,2-Dichloropropionic Acid) CASRN 75-99-0

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Dalapon (2,2-Dichloropropionic Acid) (1992b)	0.2	0.2	0.03/ 8 (NOAEL)/ 300 (10H, 10A, 3D)/ Increased kidney weight/ Paynter et al., 1960	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.9 20%	0.03 (1988e)/ 8.45 (NOAEL)/ 300 (10H, 10A, 3D)/ Increased kidney to body weight ratio/ Paynter et al., 1960	--	--	--

Table 12a. Summary of EPA Assessments: 1,2-Dibromo-3-chloropropane (DBCP) CASRN 96-12-8

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,2-Dibromo-3-chloropropane (DBCP) (1991g)	0	0.0002 (PQL)	--	B2, Probable human carcinogen (1986i guidelines)/ Potency: 1.4 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 0.00025 mg/L/ (BW)2/3/ Linearized multistage model	--	--	--	--	--

Table 12b. Summary of Assessments by Other Organizations: 1,2-Dibromo-3-chloropropane (DBCP) CASRN 96-12-8

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
1,2-Dibromo-3-chloropropane (DBCP)	--	--	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

Table 13a. Summary of EPA Assessments: 1,1-Dichloroethylene CASRN 75-35-4

Chemical (Date of regulation)	**U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)**					**U.S. EPA IRIS**		**U.S. EPA OPP**	
	MCLG mg/L	MCL mg/L (basis if MCL≠MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,1-Dichloroethylene (1987i)	0.007	0.007	0.01/ 10 (LOAEL)/ 1000 (10H, 10A, 10L)/ Liver toxicity (fatty change)/ Quast et al., 1983	C, Possible human carcinogen (1986i guidelines)	0.35 20% (also a factor of 10 for class C, possible carcinogen)	**0.05 (2002d)[46]/ 4.6 ($BMDL_{10}$)/ 100 (10H, 10A)/ Liver toxicity (fatty change)/ Quast et al., 1983**	"Suggestive evidence" of carcinogenicity but not sufficient evidence to assess human carcinogenic potential under draft 1999 Guidelines (U.S. EPA, 2002d)	--	--

[46] Using the RfD of 0.05 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value would be 0.35 mg/L (rounded to 0.4 mg/L).

Table 14a. Summary of EPA Assessments: *cis*-1,2-dichloroethylene CASRN 156-59-2

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
cis-1,2-Dichloroethylene (1991g)	0.07	0.07	0.01/ 32 (NOAEL)/ 3000 (10H, 10A, 10L, 3D)/ decreases in hematocrit/ McCauley et al., 1990	--	0.35 20%	**0.002 (2010b)[47]/ 5.1 ($BMDL_{10}$)/ 3000 (10H, 10A, 10S, 3D)/ Increased relative kidney weight in males/ McCauley et al., 1990, 1995**	Inadequate information to assess the carcinogenic potential (2005a guidelines; 2010b)	--	--

[47] The potential new MCLG could decrease based on the RfD from 2010b IRIS. The RfD is 0.002 mg/kg-d and assuming 70 kg body weight and 2 liters water intake per day, the DWEL would be 0.0595 mg/L. Using an RSC of 20% the potential new MCLG would be 0.01 mg/L.

Table 15a. Summary of EPA Assessments: *trans*-1,2-Dichloroethylene CASRN 156-60-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
trans-1,2-Dichloroethylene (1991g)	0.1	0.1	0.02/ 17 (NOAEL)/ 1000 (10H, 10A, 10S)/ Males: increases in serum alkaline phosphatase; females: decrease in relative thymus weight/ Barnes et al., 1985	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.6 20%	0.02 (2010b) [48]/ 65 ($BMDL_{1SD}$)/ 3000 (10H, 10A, 10S, 3D)/ Decrease in the number of antibody forming cells (AFCs) against sheep red blood cells (sRBC) in male mice/ Shopp et al., 1985	Inadequate information to assess the carcinogenic potential (2005a guidelines; 2010b)	--	--

[48] IRIS completed an assessment in 2010; however, the new RfD does not result in a change to the MCLG.

Table 16a. Summary of EPA Assessments: Di(2-ethylhexyl) adipate (DEHA) CASRN 103-23-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Di(2-ethylhexyl) adipate (DEHA) (1992b)	0.4	0.4	0.6/ 170 (NOAEL)/ 300 (10H, 10A, 3S and D combined)/ Body and liver weight changes in parents, reduced ossification and slightly dilated ureters in fetuses; reduced offspring weight gain, total litter weight, and litter size/ ICI, 1988a,b	C, Possible human carcinogen (1986i guidelines)/ Potency: 1.2×10^{-3} per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-1} mg/L/ (BW)2/3/ Linearized multistage model	20 20% (and a factor of 10 for class C, possible carcinogen-icity)	0.6 (1991c)/ 170 (NOAEL)/ 300 (10H, 10A, 3D)/ Body and liver weight changes in parents, reduced ossification and slightly dilated ureters in fetuses; reduced offspring weight gain, total litter weight, and litter size/ ICI, 1988a,b	C, Possible human carcinogen (1986i guidelines; 1991c)/ Potency: 1.2×10^{-3} per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-1} mg/L/ (BW)2/3/ Linearized multistage model	--	--

Table 17a. Summary of EPA Assessments: Dinoseb CASRN 88-85-7

Chemical (Date of regulation) (List A or B)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Dinoseb (1992b)	0.007	0.007	0.001/ 1 (LOAEL)/ 1000 (10H, 10A, 10L)/ Reduction in thyroid weight; endometrial hyperplasia and hypospermato-genesis; testicular degeneration/ Hazleton, 1977; Brown, 1981	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.04 20%	0.001 (1986d)/ 1 (LOAEL)/ 1000 (10H, 10A, 10L)/ Decreased pup weight during lactation period. Decreased parental weight gain/ Dow Chemical Company, 1981	D, Not classifiable as to human carcinogenicity (1986i guidelines; 1989c)	--	--

Table 18a. Summary of EPA Assessments: Dioxin (2,3,7,8-TCDD) CASRN 1746-01-6

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
2,3,7,8-TCDD (Dioxin) (1988f)	0	3×10^{-8}/ (PQL)	1×10^{-9}/ 1×10^{-6} (LOAEL)/ 1000 (10H, 10A, 10L)/ Reduced gestation index, decreased fetal weight, increased liver-to-body weight ratio, dilated renal pelvis/ Murray et al., 1979	B2, Probable human carcinogen (1986i guidelines)/ Potency: 156,000 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 2×10^{-6} mg/L/ (BW)2/3/ Linearized multistage model	3.5×10^{-8} --	7×10^{-10} (2012b)/ 2×10^{-8} / 30 (3H, 10L)/ decreased sperm count and motility in men exposed to TCDD as boys/ Mocarelli et al., 2008/ Increased TSH in neonates/ Baccarelli et al., 2008	--	--	--

Table 18b. Summary of Assessments by Other Organizations: Dioxin (2,3,7,8-TCDD) CASRN 1746-01-6

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
2,3,7,8-TCDD (Dioxin) (1988f)		4.7×10^{-10} (2010d)[49]	Likely to be carcinogenic to humans (2010d)	--	--	--	--	--	Group 1, Carcinogenic to humans (2012b)	Known to be a human carcinogen (2014)

[49] The public health goal derived by CalEPA is based on cancer potency. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 19a. Summary of EPA Assessments: Diquat CASRN 85-00-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Diquat (1992b)	0.02	0.02	0.002/ 0.22 (NOAEL)/ 100 (10H, 10A)/ Cataracts/ Colley, 1985	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.077 20%	0.0022 (1986e)/ 0.22 (NOAEL)/ 100 (10H, 10A)/ Minimal lens opacity and cataracts/ (Chevron Chemical, 1985	--	**0.005 (1995a, 2002e)[50]/ 0.5 (NOAEL)/ 100 (10H, 10A)/cataracts in females, decreased adrenal and epididymis weights in males/ Hopkins, 1990**	E, Evidence of noncarcinogenicity (1986i guidelines; 1995b)

[50] The MCLG could increase based on the RfD from OPP 1995a and 2002e. The RfD is 0.005 mg/kg-d and assuming 70 kg body weight and 2 liters water intake per day, the DWEL would be 0.175 mg/L. Using an RSC of 20% the potential new MCLG would be 0.04 mg/L.

Table 20a. Summary of EPA Assessments: Endothall CASRN 145-73-3

Chemical (Date of regulation) (List A or B)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Endothall (1992b)	0.1	0.1	0.02/ 2 (NOAEL)/ 100 (10H, 10A)/ Increased organ weight and organ-to-body weights for stomach and small intestine/ Keller, 1965	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.7 20%	0.02 (1986f)/ 100 ppm, equivalent to 2 mg/kg/day (NOEL)/ 100 (10H, 10A)/ Increased absolute and relative weights of stomach and small intestine/ Keller, 1965	--	**0.007 (2005d[51])/ 2 (LOAEL)/ 300 (10H, 10A, 3L)/ Proliferative lesions of the gastric epithelium/ Trutter, 1995**	Unlikely to be carcinogenic to humans (1999 guidelines; 2005d)

[51] Using the RfD of 0.007 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.049 mg/L (rounded to 0.05 mg/L).

Table 20b. Summary of Assessments by Other Organizations: Endothall CASRN 145-73-3

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Endothall	--	0.025 (2014)[52]	--	--	--	--	--	--	--	--

[52] The public health goal derived by CalEPA is based on noncancer effects. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 21a. Summary of EPA Assessments: Endrin CASRN 72-20-8

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Endrin (1992a)	0.002	0.002	0.0003/ 0.025 (NOAEL)/ 100 (10H, 10A)/ Mild histopathologic changes in liver, occasional convulsions/ Velsicol Chemical Corporation, 1969	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.009 20%	0.0003 (1988g)/ 0.025 (NOAEL)/ 100 (10H, 10A)/ Mild histopathologic changes in liver, occasional convulsions/ Velsicol Chemical Corporation, 1969	D, Not classifiable as to human carcinogenicity (1986i guidelines; 1988g)	--	--

Table 22a. Summary of EPA Assessments: Ethylene dibromide (EDB; 1,2-Dibromoethane) CASRN 106-93-4

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Ethylene Dibromide (EDB; 1,2-Dibromoethane) (1991g)	0[53]	0.00005 (PQL)	--	B2, Probable human carcinogen (1986i guidelines)/ Potency: 85 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 4×10^{-6} mg/L/ (BW)2/3	--	0.009 (2004)/ 27 (LOAEL)/ 3000 (10H, 10A, 10L, 10D)/ Testicular atrophy, liver peliosis, and adrenal cortical degeneration/ NCI, 1978b	Likely to be carcinogenic to humans (1999 guidelines; 2004)/ Potency: 2 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 2×10^{-4} mg/L/ (BW)3/4/ LED10 with linear extrapolation; slope factors calculated from multiple tumor sites and summed using statistically appropriate model.	--	--

[53] The current NPDWR assessment is not consistent with the 2004 IRIS assessment. The PQL is slightly greater than the 1×10^{-6} risk concentration of 2×10^{-3} mg/L.

Table 22b. Summary of Assessments by Other Organizations: Ethylene dibromide (EDB; 1,2-Dibromoethane) CASRN 106-93-4

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Ethylene dibromide (EDB; 1,2-Dibromoethane)	--	--	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

Table 23a. Summary of EPA Assessments: Fluoride CASRN 7782-41-4

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OW	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Fluoride (1986k)	4.0	4.0	No RfD[54]/ 20 mg/day (LOAEL)/(2.5H)/ crippling skeletal fluorosis/ Shapiro 1983, Koop 1984, WHO 1984	--	-- 100%	0.06[55]/ 1986g/ 0.06 (NOAEL)/ 1(1H)/ objectionable dental fluorosis/ Hodge 1950	--	0.08/(2010) 0.07 intake from drinking water + 0.01 intake from food)/ 1H Severe dental fluorosis in children Dean 1942 McClure 1943	--

[54] EPA published a secondary maximum contaminant level (SMCL) for fluoride of 2.0 mg/L to protect against dental fluorosis (an adverse cosmetic effect) (NPDWR for fluoride, April 2, 1986 (51FR: 11397)).

[55] The IRIS Substance Assessment Tracking system website (https://cfpub.epa.gov/ncea/iris2/atoz.cfm) should be consulted for the most current information on the status of this assessment.

Table 24a. Summary of EPA Assessments: Heptachlor CASRN 76-44-8

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Heptachlor (1991g)	0	0.0004 (PQL)	0.0005/ 0.15 (NOAEL)/ 300 (10H, 10A, 3D)/ Increased liver to body weight ratio in males/Witherup et al., 1955	B2, Probable human carcinogen (1986i guidelines)/ Potency: 4.5 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 8×10^{-5} mg/L/(BW)2/3/ Linearized multistage model	--	0.0005 (1987f)/ 0.15 (NOAEL)/ 300 (10H, 10A, 3D)/ Increased liver to body weight ratio in males/ Velsicol Chemical, 1955	B2, Probable human carcinogen (1986i guidelines; 1987f)/ Potency: 4.5 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 8×10^{-5} mg/L/(BW)2/3/ Linearized multistage model	0.0005 (1992c)/ 0.15 (NOAEL)/ 300 (10H, 10A, 3D)/ Liver lesions and increased relative liver weight/ Witherup et al., 1955	B2, Probable human carcinogen (1986i guidelines; 1992c)

Table 25a. Summary of EPA Assessments: Heptachlor epoxide CASRN 1024-57-3

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Heptachlor Epoxide (1991g)	0	0.0002 (PQL)	0.000013/ 0.0125 (LOAEL)/ 1000 (10H, 10A, 10L)/ Increase in liver-to-body weight ratio/ Dow Chemical Company, 1958	B2, Probable human carcinogen (1986i guidelines)/ Potency: 9.1 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 4×10^{-5} mg/L/(BW)2/3/ Linearized multistage model	--	0.000013 (1986j)/ 0.0125 (LEL)/ 1000 (10H, 10A, 10L)/ Increase in liver-to-body weight ratio/ Dow Chemical Company, 1958	B2, Probable human carcinogen (1986i guidelines; 1987g)/ Potency: 9.1 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 4×10^{-5} mg/L/(BW)2/3/ Linearized multistage model	0.000013 (1992c)/ 0.0125 (LEL)/ 1000 (10H, 10A, 10L)/ Increase in liver-to-body weight ratio/ Dow Chemical Company, 1958	B2, Probable human carcinogen (1986i guidelines; 1992c)

Table 26a. Summary of EPA Assessments: Hexachlorobenzene CASRN 118-74-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Hexachlorobenzene (1992b)	0	0.001 (PQL)	0.0008/ 0.08 (NOAEL)/ 100 (10H, 10A)/ Hepatic centrilobular basophilic chromogenesis/ Arnold et al., 1985	B2, Probable human carcinogen (1986i guidelines)/ Slope factor: 1.6 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 2×10^{-4} mg/L/ (BW)2/3/ Linearized multistage model	--	0.0008 (1988h)/ 0.08 (NOAEL)/ 100 (10H, 10A)/ Hepatic centrilobular basophilic chromogenesis/ Arnold et al., 1985	B2, Probable human carcinogen (1986i guidelines; 1989d)/ Slope factor: 1.6 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 2×10^{-4} mg/L (Based on Erturk, et al., 1986)./ (BW)2/3/ Linearized multistage model	--	B2, Probable human carcinogen (1996 guidelines; 2008b)/ slope factor 1.02 per mg/kg-d, hepatocellular carcinomas in rats orally exposed /(BW)3/4/not specified

Table 26b. Summary of Assessments by Other Organizations: Hexachlorobenzene CASRN 118-74-1

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Hexachlorobenzene	--	0.00007 [56] (2015)	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

[56] The chronic MRL is based on the same critical study, Arnold et al., 1985 that was used by EPA; however different endpoint (peribiliary lymphocytosis and fibrosis of the liver) was used compared to EPA assessments (Hepatic centrilobular basophilic chromogenesis)

Table 27a. Summary of EPA Assessments: Hexachlorocyclopentadiene CASRN 77-47-4

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Hexachlorocyclo-pentadiene (1992b)	0.05	0.05	0.007/ 7.14 (adj. NOAEL)/ 1000 (10H, 10A, 10S)/ Focal inflammation of the forestomach and stomach lesions/ SRI, 1981	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.3 20%	**0.006 (2001a)[57]/ 6 ($BMDL_{10}$)/ 1000 (10H, 10A, 3S, 3D)/ Chronic irritation of forestomach (forestomach lesions)/ Abdo et al., 1984**	Not likely to be a human carcinogen via inhalation route; Potential for carcinogenicity by the oral route is indeterminate based on a lack of data (1996 guidelines) (2001a)	--	--

[57] Using the RfD of 0.006 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.042 mg/L (rounded to 0.04 mg/L).

Table 27b. Summary of Assessments by Other Organizations: Hexachlorocyclopentadiene CASRN 77-47-4

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Hexachlorocyclopentadiene	--	0.0011 (2014)[58]	--	--	--	--	--	--	--	--

[58] The public health goal derived by CalEPA was calculated based on the NOAEL from Abdo, et al. 1984 for noncancer effects. The CalEPA assessment is more current than the IRIS assessment and uses an updated benchmark modeling approach to derive a different POD. However, CalEPA applied policies that differ from those of the EPA Office of Water so the 2001a IRIS RfD is preferred.

Table 28a. Summary of EPA Assessments: Lindane (gamma-Hexachlorocyclohexane) CASRN 58-89-9

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/ Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/ Extrapolation method
Lindane (gamma-Hexachlorocyclohexane) (1991g)	0.0002	0.0002	0.0003/ 0.33 (NOAEL)/ 1000 (10H, 10A, 10S)/ Liver and kidney toxicity/ RCC, 1983	C, Possible human carcinogen (1986i guidelines)/ Potency: 1.3 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-4} mg/L/(BW)2/3/ Linearized multistage model	0.01 20% Also factor of 10 for class C	0.0003 (1986h)/ 0.33 (NOAEL)/ 1000 (10H, 10A, 10S)/ Liver and kidney toxicity/ Zoecon Corp, 1983	--	**0.0047 (2002g)[59]/ 0.47 (NOAEL)/ 100 (10H, 10A)/ FQPA: 3 Hepatocyte hypertrophy, increased liver weight, increased platelets/ Amyes 1989a,b, 1993**	Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential (1999 guidelines; 2002f)

[59] Using the RfD of 0.0047 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.033 mg/L (rounded to 0.03 mg/L).

Table 28b. Summary of Assessments by Other Organizations: Lindane (gamma-Hexachlorocyclohexane) CASRN 58-89-9

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification			
Lindane (gamma-Hexachlorocyclohexane)	--	--	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

Table 29a. Summary of EPA Assessments: Methoxychlor CASRN 72-43-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Methoxychlor (1991g)	0.04	0.04	0.005/ 5.01 (NOAEL)/ 1000 (10H, 10A, 10D)/ Excessive loss of litters; decreased body weight/ Trutter, 1986	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.175 20%	0.005 (1990b)/5.01 (NOAEL)/ 1000 (10H, 10A, 10D)/ Excessive loss of litters/ Kincaid Enterprises, 1986	D, Not classifiable as to human carcinogenicity (1986i guidelines; 1987h)	--	--

Table 29b. Summary of Assessments by Other Organizations: Methoxychlor CASRN 72-43-5

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Methoxychlor	--	**0.00002 (2010a)[60],[61] /0.02 (LOAEL)/1000 (10A,10H, 10L)/increased prostrate and seminal vesicle weights in mice/Judy et al. 1999**	**Carcinogenicity studies are inadequate by present standards (2010a)**	--	--	--	--	--	--	--

[60] The public health goal derived by CalEPA is based on noncancer effects. The RfD-equivalent shown was calculated based on the LOAEL and UF provided by CalEPA for noncancer effects.

[61] Using the RfD of 0.00002 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.00014 mg/L (rounded to 0.0001 mg/L).

Table 30a. Summary of EPA Assessments: Oxamyl CASRN 23135-22-0

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Oxamyl (Vydate) (1992b)	0.2	0.2	0.025/ 2.5 (NOAEL)/ 100 (10H, 10A)/ decreased body weight gain/ Kennedy, 1986	E, Evidence of noncarcinogenicity (1986i guidelines)	0.9 20%	0.025 (1986m)/ 2.5 (NOEL)/ 100 (10H, 10A)/ decreased body weight gain and food consumption/ E.I. du Pont de Nemours and Company, 1972	--	**0.0069[62] (2010e)/ 0.069 ($BMDL_{10}$)/ 10 (10H)/Acetyl cholinesterase inhibition in human red blood cells**	E, Evidence of noncarcinogenicity (1986i guidelines; 2010e)

[62] The RfD for oxamyl is an acute RfD of 0.0069 mg/kg/day based on acetylcholinesterase (AChE) inhibition in human red blood cells. A chronic RfD was not derived because of the rapid recovery of AChE activity and an acute exposure based RfD that is considered protective for chronic exposure. The potential new MCLG of 0.1 mg/L is derived based on a 10 kg body weight and 1.0 L drinking water consumption and an RSC of 20% as follows: 0.0069 mg/kg/day x 0.2 x 10kg/1L = 0.0138 mg/L. An alternate potential new MCLG of 0.009 mg/L can be derived for children from birth to less than 12 months at the 90th percentile of 0.15 L/kg (U.S. EPA, 2011a Exposure Factor Handbook, based on Table 3-19) as follows: 0.0069 mg/kg/day x 0.2 x 10kg/1.5L = 0.009 mg/L.

Table 30b. Summary of Assessments by Other Organizations: Oxamyl CASRN 23135-22-0

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Oxamyl (Vydate)	--	0.006 (2009b) [63]	Classification not stated, but indicates oxamyl is not a mutagen or carcinogen (2009b)	--	--	--	--	--	--	--

[63] The public health goal derived by CalEPA is based on noncancer effects. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 31a. Summary of EPA Assessments: Pentachlorophenol CASRN 87-86-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Pentachlorophenol (1991e)	0	0.001 (PQL; analytical feasibility)	0.03/ 3 (NOAEL)/ 100 (10H, 10A)/ pigmentation of kidneys/ Schwetz et al., 1978	B2, Probable human carcinogen (1986i guidelines)/ Potency: 0.12 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3×10^{-3} mg/L/ (BW)2/3/ Linearized multistage model	1.1	0.005 (2010d)/ 1.5 (LOAEL)/ 300 (10H, 10A, 3L)/ Hepatotoxicity/ Mecler, 1996	Likely to be carcinogenic to humans (2005a guidelines; 2010d)/ Potency[58]: 0.4 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 9×10^{-7} mg/L/ (BW)3/4/ Multistage model with linear extrapolation from the POD (LED10).	0.005 (2008b)/ 1.5 (LOAEL)/ 300 (10H, 10A, 3L)/ Hepatotoxicity/ Mecler, 1996	B2, Probable human carcinogen (1986i guidelines; 2008b)/ Potency 0.07 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 5×10^{-3} mg/L/ (BW)3/4/ Linearized multistage model

[58] An IRIS assessment (U.S. EPA, 2010d) for pentachlorophenol states that under the 2005a Guidelines PCP is "likely to be carcinogenic to humans." A multistage model using linear extrapolation from the point of departure (based on increased incidence of hepatocellular and adrenal gland tumors in male mice) was performed to derive an oral slope factor of 4×10^{-1} (mg/kg-day)$^{-1}$ for PCP. The recommended slope factor should not be used with exposures greater than 0.25 mg/kg-day (the point of departure for the site with the greatest response for tPCP-exposed male mice), because above this point the slope factor may not approximate the observed dose-response relationship adequately.

Table 31b. Summary of Assessments by Other Organizations: Pentachlorophenol CASRN 87-86-5

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Pentachlorophenol	--	0.001 (2009c)[59]	Proven carcinogen in rodent studies with some epidemiological evidence (2009c)	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

[59] The public health goal derived by CalEPA is based on carcinogenic effects. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.

Table 32a. Summary of EPA Assessments: Picloram CASRN 1918-02-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Picloram (1992b)	0.5	0.5	0.07/ 7 (NOAEL)/ 100 (10H, 10A)/ Increased relative and absolute liver weights/ Dow Chemical Company, 1982	D, Not classifiable as to human carcinogenicity (1986i guidelines)	2.45 20%	0.07 (1987e)/ 7 (NOEL)/ 100 (10H, 10A)/ Increased relative and absolute liver weights/ Dow Chemical Company, 1982	--	**0.2 (1995b)[60]/ 20 (NOEL)/ 100 (10H, 10A)/ Changes in centrilobular hepatocytes/ Landry et al., 1986**	E, Evidence of noncarcinogenicity (1986i guidelines; 1995b)

[60] Using the RfD of 0.2 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 1.4 mg/L (rounded to 1 mg/L).

Table 33a. Summary of EPA Assessments: Selenium CASRN 7782-49-2

Chemical (Date of regulation)	**U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)**					**U.S. EPA IRIS**		**U.S. EPA OPP**	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Selenium (1991h)	0.05	0.05	None/ 3.2/ 15 (H, L, accounting for special status as essential element)/ Minimum dietary intake of selenium in area with chronic selenosis of 3.2 mg/day, for a 70 kg adult/ Yang et al., 1983	--	-- 50%	0.005 (1991h)/ 0.015 (NOAEL)/ 3 (3H)/ Clinical selenosis/ Yang et al., 1989	D, Not classifiable (1986i guidelines; 1990d)	--	--

Table 33b. Summary of Assessments by Other Organizations: Selenium CASRN 7782-49-2

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)/ Tolerable Upper Intake Level/ Water Ingestion Rate/ Effect/ Citation	Cancer classification (year)			
Selenium	--	0.005 (2010b)	Not associated with increases in human cancer rates. May have cancer protective properties (2010b)	0.4 mg/d upper tolerable intake (2011c, WHO)	Does not appear to be carcinogenic (2011c, WHO)	**0.05 (2014a)[61]/ 0.4 mg/day (Upper Limit);0.2 (default allocation for drinking water);1.5 L/day/ Chronic selenosis/ IOM 2000**	--	--	--	--

[61] Utilizing the IOM (2000) Tolerable Upper Intake Level (UL) of 0.4 mg/day for adults with critical effect of clinical selenosis the MCLG could decrease. The potential new MCLG would be 0.04 mg/L using 0.4 mg/day or 0.2 mg/L assuming 2L daily water consumption and a 20% RSC.

Table 34a. Summary of EPA Assessments: Styrene CASRN 100-42-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Styrene (1991g)	0.1	0.1	0.2/ 200 (NOAEL)/ 1000 (10H, 10A, 10S)/ Reduced red blood cells, iron deposits in liver/Quast et al., 1979	C, possible human carcinogen (1986i guidelines)/ Potency: 3×10^{-2} per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 1×10^{-2} mg/L/ (BW)2/3/ Linearized multistage model	7 20%	0.2 (1985d) / 200 (NOAEL)/ 1000 (10H, 10A, 10S)/ Reduced hemoglobin and red blood cells; iron deposits in liver/ Quast et al., 1979	--	--	--

Table 34b. Summary of Assessments by Other Organizations: Styrene CASRN 100-42-5

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Styrene	No intermediate or chronic oral MRL (2010a)	**0.007 mg/kg/d (2010c)[62]**	**Sufficient evidence that styrene causes cancer in animals and limited evidence in humans (2010c)[63]**	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)	--	Reasonably anticipated to be a human carcinogen (2014)

[62] The public health goal derived by CalEPA is based on cancer potency. The RfD-equivalent shown was calculated based on the NOAEL and UF provided by CalEPA for noncancer effects.
[63] The potential new MCLG could be 0 mg/L based on a possible human carcinogen.

Table 35a. Summary of EPA Assessments: Thallium CASRN 7440-28-0

Chemical (Date of regulation)	**U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)**					**U.S. EPA IRIS**		**U.S. EPA OPP**	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Thallium (1992b)	0.0005	0.002 (PQL)	0.00007/ 0.25 (NOAEL)/ 3000 (10H, 10A, 10S, 3D)/ No treatment related effects/ Stolz et al., 1986	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.002 20%	No RfD derived due to poor quality of data (2009a)	Inadequate information to assess carcinogenic potential (2005a guidelines; 2009a)	--	--

Table 36a. Summary of EPA Assessments: Toluene CASRN 108-88-3

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Toluene (1991g)	1	1	0.2/ 223 (NOAEL)/ 1000 (10H, 10A, 10S)/ Increased kidney weight/ NTP, 1990	D, Not classifiable as to human carcinogenicity (1986i guidelines)	7 20%	**0.08 (2005c)[64]/ 238 (BMDL)/ 3000 (10H, 10A, 10S, 3D)/ Increased kidney weights/ NTP, 1990**	Data are inadequate to assess carcinogenic potential (2005a guidelines; 2005c)	--	--

[64] Using the RfD of 0.08 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.56 mg/L (rounded to 0.6 mg/L).

Table 36b. Summary of Assessments by Other Organizations: Toluene CASRN 108-88-3

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Toluene	--	--	--	--	--	0.06 (2014b)	Not classifiable due to insufficient animal and human carcinogenicity data (2014b)	--	--	--

Table 37a. Summary of EPA Assessments: Toxaphene CASRN 8001-35-2

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Toxaphene (1991g)	0	0.003 (PQL)	0.0004/ 0.36 (NOAEL)/ 100 (10H, 10A, 10 MF for neurodevelop mental and immunological datagaps)/ Histological changes in liver, kidney, and thyroid/ Chu et al., 1986, 1988	B2, Probable human carcinogen (1986i guidelines)/ Potency: 1.1 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 3 x 10^{-4} mg/L/ (BW)2/3/ Linearized multistage model	--	--	B2, Probable human carcinogen (1986i guidelines; 1987k)	--	--

Table 37b. Summary of Assessments by Other Organizations: Toxaphene CASRN 8001-35-2

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Toxaphene	0.002 intermediate (2010b)	--	--	--	--	--	--	--	--	Reasonably anticipated to be a human carcinogen (2014)

Table 38a. Summary of EPA Assessments: 2,4,5-Trichlorophenoxypropionic Acid (2,4,5-TP; Silvex) CASRN 93-72-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
2,4,5-TP (Silvex; 2,4,5-Trichlorophenoxy propionic Acid) (1991g)	0.05	0.05	0.008/ 0.75 (NOAEL)/ 100 (10H, 10A)/ Histopatholog-ical changes in the liver/ Mullison, 1966	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.3 20%	0.008 (1988c)/ 0.75 (NOAEL)/ 100 (10H, 10A)/ Histopathological changes in the liver/ Mullison, 1966; Gehring and Betso, 1978	D, Not classifiable (1986i guidelines; 1987a)	--	--

Table 38b. Summary of Assessments by Other Organizations: 2,4,5-Trichlorophenoxypropionic Acid (2,4,5-TP; Silvex) CASRN 93-72-1

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
2,4,5-TP (Silvex; 2,4,5-Trichlorophen-oxypropionic Acid)	--	0.0003 (2014)	Primarily negative animal carcinogenicity, and mixed epidemiology insufficient basis to serve as basis for PHG (2014)	--	--	--	--	--	--	--

Table 39a. Summary of EPA Assessments: 1,2,4-Trichlorobenzene CASRN 120-82-1

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,2,4-Trichlorobenzene (1992b)	0.07	0.07	0.01/ 14.8 (NOAEL)/ 1000 (10H, 10A, 10S)/ Increased adrenal weights; vacuolization of zona fasciculata in the cortex/ Robinson et al., 1981	D, Not classifiable as to human carcinogenicity (1986i guidelines)	0.35 20%	0.01 (1991a)/ 14.8 (NOAEL)/ 1000 (10H, 10A, 10S/D)/ Increased adrenal weights; vacuolization of zona fasciculata in the cortex/ Robinson et al., 1981	Not classifiable as to human carcinogenicity[65] (1988b)	--	--

[65] U.S. EPA (2009b) has concluded that 1,2,4-trichlorobenzene is "Likely to be carcinogenic to humans" (2005a guidelines)/ Slope factor 0.029 per mg/kg-d/POD 3.5 mg/kg-day ($BMDL_{10HED}$)/ increased hepatocellular carcinoma/0.1/ $BMDL_{10HED}$

Table 39b. Summary of Assessment by Other Organizations: 1,2,4-Trichlorobenzene CASRN 120-82-1

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/ Effect/ Citation	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
1,2,4-Trichlorobenzene	**0.1 (2010c)[66] /13.33 ($BMDL_{10}$)/ 100 (10A, 10H)/hepatocellular hypertrophy in male rats/ Moore at al. 1994**	--	--	--	--	--	--	--	--	--

[66] Using the MRL of 0.1 mg/kg/day and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 0.7 mg/L.

Table 40a. Summary of EPA Assessments: 1,1,1-Trichloroethane CASRN 71-55-6

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,1,1-Trichloroethane (1985b)	0.2	0.2	0.035/ 35.1 (LOAEL) 1000 (10H, 10A, 10L)/ Histological changes in liver/ McNutt et al., 1975	D, Not classifiable as to human carcinogenicity (1986i guidelines)	1 20%	**2.0 (2007f)[67]/ 2155 ($BMDL_{10}$)/ 1000 (10H, 10A, 3S, 3D)/ Reduced body weight/ NTP, 2000**	Inadequate information to assess carcinogenic potential (2005a guidelines; 2007f)	--	--

[67] Using the RfD of 2.2 mg/kg/day (rounded to 2.0 mg/kg/day) and assuming 70 kg body weight, 2 L/day water consumption, and a 20% RSC, a potential new MCLG derived from this value is 14 mg/L.

Table 41a. Summary of EPA Assessments: 1,1,2-Trichloroethane CASRN 79-00-5

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
1,1,2-Trichloroethane (1992b)	0.003	0.005 (PQL)	0.004/ 4 (NOAEL) 1000 (10H, 10A, 10S)/ Adverse effects on liver, depressed humoral immune status/ Sanders et al., 1985; White et al., 1985	C, Possible human carcinogen (1986i guidelines)/ Potency[68]: 0.091 per mg/kg/day; Drinking water concentration at 10^{-5} risk level: 0.004 mg/L/ (BW)2/3/ Linearized multistage model	0.137 20% Also factor of 10 for class C	0.004 (1988a)/ 3.9 (NOAEL)/ 1000 (10H, 10A, 10S)/ Clinical serum chemistry/ Sanders et al., 1985; White et al., 1985	C, Possible human carcinogen (1986i guidelines; 1986a)/ Potency: 0.057 per mg/kg/day, Drinking water concentration at 10^{-5} risk level: 0.006 mg/L/ Based on hepatocellular carcinomas in mice (NCI, 1978a)/ (BW)2/3/ Linearized multistage model	--	--

[68] The term "potency" refers to either the q1* or slope factor depending on the modeling approach that was used. In some cases the summary document did not report the potency estimate. In such cases, the potency was back-calculated from reported unit risks or risk specific concentrations to facilitate data comparisons.

Table 42a. Summary of EPA Assessments: Xylenes (Total) CASRN 1330-20-7

Chemical (Date of regulation)	U.S. EPA/OW National Primary Drinking Water Regulation (NPDWR)					U.S. EPA IRIS		U.S. EPA OPP	
	MCLG mg/L	MCL mg/L (basis if MCL≠ MCLG)	RfD (mg/kg/day)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	DWEL (mg/L) & RSC	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method	RfD (mg/kg/day) (year)/ Point of Departure/ UF (breakdown of UFs)/Effect/ Citation	Cancer classification (Year of guidelines used)/quantitative assessment/ adjustment factor/Extrapolation method
Xylenes (Total) (1991g)	10	10	1.79/ 179 (adj. NOAEL)/ 100 (10H, 10A)/ decreased body weight gains/ NTP, 1986	D, Not classifiable as to human carcinogenicity (1986 guidelines)	63 20%	**0.2 (2003d)[69], 179 (adj. NOAEL)/ 1000 (10H, 10A, 10D)/ decreased body weight gains/ NTP, 1986**	Data are inadequate to assess carcinogenic potential (1999 guidelines; 2003d)	--	--

[69] The MCLG could decrease based on the RfD from IRIS 2003d. Based on RfD of 0.2 mg/kg-d and assuming 70 kg body weight and 2 liters water intake per day, the DWEL would be 7 mg/L, and using a 20% RSC, the potential new MCLG would be 1 mg/L.

Table 42b. Summary of Assessments by Other Organizations: Xylenes (Total) CASRN 1330-20-7

Chemical	ATSDR	CalEPA		WHO Includes JECFA, JMPR, CICAD, EHC		Health Canada		NAS (year)	IARC (year)	NIEHS (year)
	MRL mg/kg/day (year)	RfD mg/kg/d (year)	Cancer classification (year)	Tolerable Daily Intake (TDI) mg/kg/day (year)	Cancer Classification (year)	Maximum Acceptable Concentration (MAC) mg/L (year)	Cancer classification (year)			
Xylenes (Total)	--	--	--	--	--	0.09 (2014b);	Not classifiable (2014b)	--	--	--

APPENDIX C - HEALTH EFFECTS OF FLUORIDE

As a result of the first Six-Year Review of the fluoride NPDWR (67 FR 19030 (U.S. EPA, 2002) (preliminary); 68 FR 42908 (U.S. EPA, 2003) (final)), EPA requested that the National Research Council (NRC) of the National Academies of Science (NAS) conduct a review of the health and exposure data on orally ingested fluoride. In 2006, the NRC published the results of its review in a report entitled, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*. Based on its review, NRC concluded that severe dental fluorosis is an adverse health effect when it causes both a thinning and pitting of the enamel, a situation that compromises the function of the enamel in protecting the tooth from decay and infection. In addition, the committee examined the scientific data on the impact of fluoride on the strength and structure of bone and the majority concluded that the MCLG "is not likely to be protective against bone fractures." The NRC recommended that EPA develop a dose-response assessment for severe dental fluorosis as the crtitical effect and update an assessment of fluoride exposure from all sources.

During the Six-Year Review 2, the Agency was in the process of developing a dose-response assessment of the non-cancer impacts of fluoride on severe dental fluorosis and the skeletal system. In addition, EPA was updating its evaluation of the relative source contribution (RSC) of drinking water to total fluoride exposure considering the contributions from dental products, foods, pesticide residues, and other sources such as ambient air and medications. These assessments were not completed at the time of the Six-Year Review 2; thus, no action was taken under the Six-Year Review 2 (75 FR 15500, U.S. EPA, 2010c).

In 2010, EPA published fluoride health assessments (U.S. EPA, 2010a; 2010b). In the "Dose Response Analysis for Non-Cancer Effects" report (U.S. EPA, 2010a), EPA derived a total reference dose (RfD) of 0.08 milligrams per kilograms per day (mg/kg/day) based on studies of dental fluorosis among children in the 6 months to 14 year age group (U.S. EPA, 2010a). The RfD is an estimate of the fluoride dose that will protect against the critical health endpoint – severe dental fluorosis – as well as clinical stage II skeletal fluorosis and skeletal fractures while allowing for a fluoride exposure adequate to protect against tooth decay for children and adults. Confidence in the RfD is considered to be medium because of the challenges of converting concentration-response data from the Dean (1942) study to dose estimates for the RfD derivation (U.S. EPA, 2010a). The RfD includes a 0.07 mg/kg/day dose for fluoride in water and 0.01 mg/kg/day for fluoride in food at the time the data on severe dental fluorosis were collected. The 0.07 mg/kg/day dose for fluoride in water was based on a benchmark dose 95 percent lower bound (BMDL) of 1.87 mg/L that is associated with a 0.5 percent incidence of severe dental fluorosis in the study by Dean (1942).

In the "Exposure and Relative Source Contribution Analysis" report (U.S. EPA, 2010b), EPA revised its relative source contribution (RSC) estimates, which range from 40% to 70% across different age cohorts (U.S. EPA, 2010b). The higher RSC values are associated with infants fed with powdered formula or concentrate reconstituted with residential tap water (70%) and with adults (60%). These RSC values are lower than the RSC of 100% used to derive the original MCLG because of the increase in daily exposure to fluoride in other sources such as commercial beverages, solid foods, fluoride-containing dental products, pesticide residues, and other sources such as ambient air.

EPA used the BMDL of 1.87 mg/L as the Drinking Water Equivalent Level for fluoride. The EPA's (2010b) RSC estimates were derived using the national mean fluoride concentration in public water supplies at the time of that assessment (0.87 mg/L). Most community water systems (CWSs) that provide fluoridation of their drinking water have already lowered their fluoridation level to a single level of 0.7 mg/L from a previous range of 0.7 to 1.2 mg/L to accommodate the updated PHS recommendation (U. S. Department of Health and Human Services, 2015). The U.S. Food and Drug Administration (FDA) also issued a letter to bottled water manufacturers recommending that they not add fluoride to bottled water in excess of the revised PHS recommendations (FDA, 2015). In addition, the FDA stated it intends to revise the quality standard regulation for fluoride added to bottled water to be consistent with the updated PHS recommendation. Therefore, EPA anticipates that a significant portion of the population's exposure to fluoride in drinking water, as well as some commercial beverages that use fluoridated water from CWSs and certain bottled water, has already been or will be reduced. This information will likely be useful in re-evaluating the RSC. The Six-Year Review 3 monitoring data for fluoride do not reflect the full impact of the change in the PHS fluoridation level. Therefore, EPA currently cannot use the Six-Year Review 3 monitoring data to project a MCLG based on the RfD at this time. In addition to the tooth and bone effects, the NRC also evaluated the impact of fluoride on reproduction and development, neurotoxicity and behavior, the endocrine system, genotoxicity, cancer and other effects. The NRC (2006) concluded that the available data were inadequate to determine if a risk for effects on these endpoints exists at an MCLG of 4.0 mg/L and made recommendations for additional research. After considering the genotoxicity data, cancer studies in humans and animals, and studies of mode of action in cell systems, the NRC determined that the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed. NRC recommended that EPA await the results and publication of an in-process hospital-based, case-control study of osteosarcoma and fluoride exposure from the Harvard School of Dental Medicine before determining if an Agency update of the cancer risk assessment for fluoride is necessary. One paper from this study (Bassin et al., 2006) was published after the NRC report but the data were included in the NRC report based on the author's dissertation. Bassin et al. (2006) showed an age-related relationship between osteosarcoma in young male subjects (< 20 years) and estimated fluoride exposures from drinking water. The NRC classified the study as having "multiple limitations in design, analysis and presentation of findings." A subsequent study from the same project (Kim et al., 2011) found there were no significant differences between the fluoride levels in bone from 142 individuals with osteosarcoma and 52 controls with cancers at other sites. Two hundred tumor-adjacent bone samples and 57 iliac crest bone samples were analyzed for their fluoride content. Both conditional and unconditional logistic regressions were used to analyze the data and determine the odds ratio for a correlation between the bone fluoride levels and the risk for osteosarcoma. The odds ratio adjusted for age, gender, and a history of broken bones was 1.33 (CI 0.56-3.15).

Based upon the recommendations of the NRC, EPA has evaluated dental fluorosis as a critical endpoint of concern for this Six-Year Review (U.S. EPA, 2010a; 2010b). EPA also reviewed recent publications on the impact of fluoride on reproduction and development, neurotoxicity and behavior, the endocrine system and cancer as they become available. EPA noted limitations in some of these studies such as lack of details and confounding factors. Overall, the new data were not sufficient to alter the NRC conclusion that severe dental fluorosis is the critical health effects endpoint for the MCLG. While EPA has evaluated the available health effects and exposure information related to fluoride, the Agency also recognizes that new studies on fluoride are currently being performed. One example is a National Toxicology Program (NTP) systematic review of animal studies that examined the impact of fluoride on learning and memory (NTP,

2016). For more information about fluoride developmental neurotoxicity, visit the National Toxicology Program website at https://ntp.niehs.nih.gov/pubhealth/hat/noms/fluoride/neuro-index.html.

Examples of other relevant new studies published after the U.S. EPA (2010a; 2010b) and NRC (2006) publications are provided below.

- Blakely et al. (2014) conducted a study to examine whether there was a relationship between drinking water fluoride and an increased risk of primary bone cancer (osteosarcoma or Ewing sarcoma). Geographical information system methodologies were used to assign the drinking water fluoride levels to the cancer cases. The cases were limited to individuals ages birth to 49 years. The findings of Blakely et al. (2014) study provided no evidence that levels of fluoride (0 to 1.268 mg/L) in drinking water, including systems that fluoridated, lead to greater risk of either osteosarcoma or Ewing sarcoma. Ewing sarcoma is a tumor that usually begins in bone or the soft tissue surrounding the bone of children, often during periods of rapid bone growth.

- A meta-analysis (Choi et al., 2012) focused on studies conducted in rural China (with drinking water fluoride concentrations up to 11.5 mg/L) and found an association between high fluoride exposures and lower IQ scores. The author noted the low quality of the studies included in the meta-analysis and the inability to rule out other explanations. Another study by Choi et al. (2015) found that 51 children with moderate or severe dental fluorosis scored significantly lower in total and backward digit span tests (a test used to assess short-term memory and working memory) than those with no or questionable fluorosis; 60% of those tested had moderate or severe dental fluorosis. The authors reported that the levels of other contaminants that might have neurological impact were low in the area (lead and arsenic specified), but did not mention the iodine status for the children or the drinking water levels for manganese. The tests focused on nonverbal measures of learning and memory because most of the available neurophysiological tests were not in Chinese. Six measures of learning and memory as represented in 14 subtests were selected. Only one (digit span) displayed a significant difference between those with normal/questionable fluorosis (n=8) and those with moderate/severe fluorosis (n=26). The digit span test is described as requiring the child to repeat a strings of digits forward and backward. Those with moderate/severe dental fluorosis had significantly lower scores ($p<0.05$) in the backward and total digit span scores than those with normal/questionable fluorosis. Although the findings of Choi et al. (2015) are noteworthy, a limitation of the study is its statistical weight because of the small size of the study population (n=51), and because of the fact that significance was achieved for only two components of the 14 subtests administered.

- Broadbent et al. (2015) conducted a study in New Zealand and reported no association between high fluoride exposures and lower I.Q. scores in children.

- Peckham et al. (2015) reported a higher prevalence of hypothyroidism among primary care practices located in fluoridated[70] versus non-fluoridated areas in England. However, exposure to fluoridated water was based on the location of the physician's practice, not on the patient's residence and no attempt was made to control for other confounding factors, such as iodine sufficiency. Iodine deficiency is common in England (Grimes, 2015).

- Malin et al. (2015) found a higher prevalence of reported attention deficit hyperactivity disorder (ADHD) in states with higher percentages of persons receiving fluoridated water. Exposure to fluoridated water was measured at the state level and based on the CDC census which includes both naturally fluoridated systems and systems that supplement the natural fluoride with a certified additive to achieve the fluoride level established by the state for fluoridation. In addition, the study did not control for other possible factors that may affect ADHD, such as prenatal exposures to alcohol or tobacco, premature delivery, low birth weight, and exposure to other environmental factors such as lead.

- The National Toxicology Program (NTP) conducted a systematic review of animal studies that examined the impact of fluoride on learning and memory (NTP, 2015; 2016). From among 4656 studies identified via database searches there were 68 studies in mice and rats that examined exposures from drinking water or diet; 48 of those studies examined effects on learning and memory and 16 of those assessed exposures during development. The dose range tested was 0.12 to 40 mg/kg/day, all greater than the 0.08 mg/kg/day RfD for severe dental fluorosis in humans identified in the EPA assessment (U.S. EPA, 2010a). NTP (2015; 2016) concluded that there was low to moderate confidence suggestive of effects on learning and memory with the moderate finding applicable to animals exposed as adults and the low finding applicable to the developmental studies.

- A study by Garcia-Perez et al. (2013) strengthens the link between severe dental fluorosis and carries. The study was conducted in two low socioeconomic communities in Mexico using 457 children (ages 8 -12 years). The mean decayed missing and filled teeth (D_3MFT) and the dental fluorosis score as determined by the Thylstrup-Fejerskov Index (TFI) was highly significant ($P<0.0001$) when children (369) with scores< 4 were compared to children with scores >4 (88). Fluoride exposures were from both the drinking water and salt fluoridation. Under the TFI procedure scores >4 are those that require pitting of the tooth enamel (U.S. EPA, 2010a).

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