SCREENING-LEVEL EVALUATION FOR THE HUMAN HEALTH RISK ASSESSMENT—LOTT CLEAN WATER ALLIANCE RECLAIMED WATER INFILTRATION STUDY

Prepared for:

LOTT CLEAN WATER ALLIANCE
500 Adams Street NE
Olympia, WA

May 29, 2020

INTERTOX, INC.
600 Stewart St.
Suite 1101
Seattle, WA 98101

206.443.2115 phone
206.443.2117 facsimile

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

ADHD	Attention Deficit Hyperactivity Disorder
ADI	Acceptable Daily Intake
ATSDR	Agency for Toxic Substances and Disease Registry
BIRWP	Budd Inlet Reclaimed Water Plant
BMDL	Benchmark Dose Level
BMDS 2.3	Benchmark Dose Software 2.3
BPA	Bisphenol A
BW	Body Weight
CCL	Contaminant Candidate List
CCRIS	Chemical Carcinogenesis Research Information System
CHL	Chinese Hamster Lung
CHO	Chinese Hamster Ovary
COI	Chemical of Interest
CPDB	Carcinogenic Potency Database
CSF	Cancer Slope Factor
DACT	Diaminochlorotriazine
DEA	Desethylatrazine
DEET	N,N-Diethyl-meta-toluamide
DIA	Deisopropylatrazine
DWEL	Drinking Water Equivalent Level
EC	European Commission
EDC	Endocrine Disrupting Compound
EFSA	European Food Safety
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPC	Exposure Point Concentration
EU	European Union Panel
FA	Fraction Available
FDA	U.S. Food and Drug Administration
GD	Gestation Day
GW	Groundwater
HA	Health Advisory
HBV	Health Based Value
HCN	Health Council of the Netherlands

HDPE	High-Density Polyethylene Pipe
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
HHRA	Human Health Risk Assessment
HRL	Health Reference Level
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	Lowest Observed Adverse Effect Level
LOTT	LOTT Clean Water Alliance
MADL	Maximum Acceptable Dose Level
MCC	Mass of Colonic Contents
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MDH	Minnesota Department of Health
MIC	Minimum Inhibitory Concentration
MLA	Mouse Lymphoma Assay
MRL	Minimal Risk Level
MTCA	Model Toxics Control Act
MTD	Maximum Tolerated Dose
MWRWP	Martin Way Reclaimed Water Plant
NA	Not Analyzed
NCI	National Cancer Institute
NDMA	N-Nitroso dimethylamine
nHRL	Noncancer Human Risk Limit
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NLM	National Library of Medicine
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSRL	No Significant Risk Level
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment
PFAS	Polyfluoroalkyl substances
PFBA	Perfluoro butanoic acid
PFOA	Perfluoro octanoic acid

PFOS	Perfluoro octanesulfonate
PHG	Public Health Goal
PND	Postnatal Day
PPCP	Pharmaceuticals and Personal Care Product
RfD	Reference Dose
RM	River Mile
RSL	Regional-Screening Level
RWIS	Reclaimed Water Infiltration Study
SaF	Safety Factor
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products
SCE	Sister Chromatid Exchange
SDWA	Safe Drinking Water Act
SF	Slope Factor
SMILES	Simplified Molecular Input Line Entry Specification
TCEP	Tris(2-carboxyethyl) phosphine
TCPP	Tris(1-chloro-2-propyl) phosphate
TDCPP	Tris(1,3-dichloroisopropyl) phosphate
TDI	Tolerable Daily Intake
TTC	Threshold of Toxicologic Concern
U.S. EPA	United States Environmental Protection Agency
UCMR	Unregulated Contaminant Monitoring Rule
UDS	Unscheduled DNA Synthesis
UF	Uncertainty Factor
VSD	Virtually Safe Dose
WHO	World Health Organization

EXECUTIVE SUMMARY

The LOTT Clean Water Alliance (LOTT) Reclaimed Water Infiltration Study (RWIS) is intended to evaluate if there are potential risks associated with use of reclaimed water for groundwater replenishment due to residual chemicals that may remain in reclaimed water after treatment. To assist with this evaluation, a human health risk assessment (HHRA) was initiated. The HHRA includes an initial screening-level evaluation that applies conservative (i.e., health protective) assumptions intended to overestimate potential human health risks in order to identify those chemicals that warrant more detailed evaluation of potential exposures and health risks in the HHRA. The results of this screening-level evaluation are described here.

Per U.S. EPA and other agencies, the goal of screening approaches is to identify areas, contaminants, or conditions that require further attention and to "screen out" those that are highly unlikely to be of concern. To conduct the screening-level evaluation, maximum-detected concentrations of chemicals of interest (COIs), consisting of residual chemicals and polyfluoroalkyl substances (PFAS) detected in reclaimed water or porewater in Tasks 1 and 2 of the RWIS, were compared to risk-based decision guides, specifically drinking water equivalent levels (DWELs) derived from human health risk-based acceptable daily intakes (ADIs). While detection of chemicals at concentrations above risk-based decision guides does not automatically trigger a response action, exceeding such concentrations suggests that further evaluation of the potential risks posed by the chemicals is appropriate.

To determine whether detected concentrations of COIs in drinking water could pose a significant health risk to people if they consumed the water, the availability of published ADIs or corresponding DWELs, such as U.S. EPA Maximum Contaminant Levels (MCLs) in drinking water, was determined. Where existing risk-based decision guides were not available, methodologies developed by U.S. EPA and other agencies to establish levels of environmental contaminants that are not likely to be associated with adverse health effects were applied to determine values based on published toxicity data or therapeutic dosing information (for pharmaceuticals), following a decision tree approach.

Identified or derived ADIs are assumed to represent the amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (i.e., chronically) for noncarcinogens or for a lifetime for carcinogens, without suffering a deleterious effect, and to be health protective for all members of the population. DWELs in ng/L (equivalent to a part per trillion or ppt) were derived from ADIs assuming that a person consumes a daily dose equal to the ADI in drinking water. To derive DWELs, an intake of one liter of drinking water per day by a child weighing 10 kg was assumed; this is a conservative assumption as the rate of water ingestion per unit of body weight generally decreases with age.

Fifteen compounds were detected at least once in reclaimed water or porewater at a concentration in excess of their DWELs. These compounds are recommended for consideration in the HHRA. Since these compounds include four hormones and two PFAS, and since DWELs for compounds in these

chemical classes are quite low, inclusion of all hormones and PFAS analyzed in the RWIS (five additional hormones and 11 additional PFAS) in the HHRA is recommended. To provide a conservative assessment, inclusion of 14 additional compounds that were detected at a maximum concentrations at or above 10% of their DWEL is also recommended.

Overall, based on the results of this screening-level evaluation, nine hormones, 16 Pharmaceuticals and Personal Care Products (PPCPs) and other personal product ingredients, seven industrial chemicals or pesticides, and 13 PFAS (45 compounds total), are recommended for consideration for inclusion in the HHRA.

This screening-level evaluation is conducted using conservative assumptions about the concentrations to which persons could be exposed (i.e., the assessment assumes that, every day, a person could drink their daily per capita amount of drinking water containing the maximum concentration of each COI that was detected in reclaimed water or porewater). Repeated daily exposure to concentrations of this magnitude and at this rate from reclaimed water is unlikely. However, because of the conservative methods applied, if detected concentrations of a compound do not exceed the DWEL (or are at <10% of their DWEL), significant human health risks from exposure to these compounds in reclaimed water is extremely unlikely. The HHRA will more closely investigate potential exposure scenarios and derive realistic estimates of human exposure, as well as more closely investigate the toxicological hazards of COIs.

1.0 INTRODUCTION

The LOTT Clean Water Alliance (LOTT) provides services to treat and manage wastewater for the urban areas of Lacey, Olympia, and Tumwater in Thurston County, Washington (at the southern end of Puget Sound). Since 2006, LOTT has produced reclaimed water that is used for irrigation and other non-drinking purposes. LOTT has undertaken a Reclaimed Water Infiltration Study (RWIS) to improve understanding of which chemicals may exist in LOTT's reclaimed water after treatment and what happens to them over time, assess the potential effects of these chemicals on human health and the environment, and provide local scientific data and community perspectives to help policymakers make informed decisions about future reclaimed water treatment.

In Tasks 1 and 2 of the RWIS, samples of reclaimed water, porewater, effluent water, groundwater, and surface water were collected from 2013-2018 and analyzed for residual chemicals and other water quality indicators. To understand the significance of detected concentrations with regard to potential human health risks, a human health risk assessment (HHRA) was initiated. The HHRA includes an initial screening-level evaluation that applies conservative (i.e., health protective) assumptions intended to overestimate potential human health risks, in order to identify those chemicals that warrant more detailed evaluation of potential exposures and health risks. The methods and results of the screening-level evaluation are presented here.

Per U.S. EPA and other agencies, the goal of screening approaches is to identify areas, contaminants, or conditions that require further attention and to "screen out" those that are highly unlikely to be of concern. While chemical concentrations above a screening level do not automatically trigger a response action, exceeding a risk-based screening level suggests that further evaluation of the potential risks posed by the chemicals is appropriate. Based on the results of this assessment, a subsequent HHRA will be conducted.

1.1 Objectives of the Screening-Level Evaluation

As described in the Scope of Work for the HHRA, the goals of the screening-level evaluation are to:

- Compare maximum-detected concentrations of chemicals of interest (COIs), including residual chemicals and polyfluoroalkyl substances (PFAS), detected in reclaimed water (including porewater) in Tasks 1 and 2 of the RWIS to risk-based decision guides, specifically drinking water equivalent levels (DWELs) derived from human health risk-based acceptable daily intakes (ADIs).
- Identify compounds that exceed DWELs as chemicals to be considered further in the HHRA (Task 3.1.2), and assess whether any other chemicals that do not exceed DWELs warrant consideration for inclusion in the HHRA.

The steps conducted to meet these goals in the screening-level evaluation are described in the following sections.

1.2 Document Overview

The subsequent sections of this document are organized as follows:

- **Data Evaluation and Hazard Characterization (Section 2.0).** This section describes the data used to conduct the screening-level evaluation, outlines the process used to select chemicals of interest (COIs) for purposes of the screening-level evaluation, and identifies the COIs.
- **Exposure Assessment (Section 3.0).** This section identifies exposure point concentrations (EPCs) for use in the screening-level evaluation. For purposes of this step, the EPC for each COI is assumed to be the maximum concentration measured in reclaimed water or porewater at any sampling location as determined from the Task 1 and 2 (Water Quality Characterization) findings.
- **Toxicity Assessment (Section 4.0).** This section establishes the relative toxicity of the COIs by identifying risk-based decision guides (i.e., acceptable daily intakes, or ADIs) for each compound. Corresponding DWELs are derived from ADIs based on a conservative estimate of the average daily drinking water rate.
- **Risk Characterization (Section 5.0).** This section compares the maximum-detected concentrations of the COIs to DWELs, to identify those that may warrant more detailed evaluation in the HHRA. In addition, this section assesses whether any chemicals that do not exceed DWELs warrant consideration for inclusion in the HHRA.
- **Conclusions and Recommendations (Section 6.0).** This section summarizes the results of the screening-level evaluation, and provides recommendations for further evaluation.
- **References (Section 7.0).** This section provides the references used to conduct the evaluation.
- **Appendix A.** This appendix summarizes maximum-detected concentrations of COIs in reclaimed water and in porewater, as well as in effluent water, groundwater, and surface water, and compares these to DWELs.
- **Appendix B.** This appendix summarizes the identified or derived risk-based decision guides for each COI and the corresponding DWELs.

2.0 DATA EVALUATION AND HAZARD CHARACTERIZATION

The objective of the data evaluation and hazard characterization step is to review the available data for conducting the screening-level evaluation and identify COIs to be evaluated in the screening-level evaluation. This section of the screening-level evaluation addresses the following:

- Site description and identification of areas and media of interest
- Evaluation of relevant datasets
- Identification of COIs for the screening-level evaluation

Results of this step are discussed below.

2.1 Site Description and Identification of Areas and Media of Interest

In Tasks 1 and 2 of the RWIS, samples of reclaimed water and porewater were collected and analyzed for residual chemicals and other water quality indicators.

Samples of reclaimed water were collected at the Budd Inlet Reclaimed Water Plant (BIRWP), the Martin Way Reclaimed Water Plant (MWRWP), and the Hawks Prairie Reclaimed Water Basin 4, to identify chemicals present in LOTT's reclaimed water and to assess the effectiveness of treatment performance on these chemicals (HDR, 2017c). Specifically:

- Sampling at the BIRWP was of Class A Reclaimed Water produced at the BIRWP, prior to entering the downtown Olympia reclaimed water distribution system. Samples were collected at the Autosampler port normally used by LOTT for Class A Reclaimed Water quality monitoring. Sampling was conducted on November 13, 2014, February 18, 2015, May 20, 2015, and August 19, 2015.
- Sampling at the MWRWP was conducted on November 12, 2014, February 17, 2015, May 20, 2015, and October 7, 2015, and consisted of the following:
  - Class A Reclaimed Wwater produced at the MWRWP treatment plant, prior to leaving the plant site, sampled at the Autosampler port normally used by LOTT for Class A reclaimed water quality monitoring.
  - Reclaimed water at the inflow point to the constructed wetlands at LOTT's Hawks Prairie site (i.e., at the end of the conveyance line that extends from the MWRWP to the Hawks Prairie site) ("Pre-Wetlands).
  - Reclaimed water that has been conveyed through the constructed wetlands, sampled at the inflow point to the infiltration basins at LOTT's Hawks Prairie site (i.e., water flowing out of the high-density polyethylene (HDPE) distribution header pipe lining the active infiltration basin) ("Post-Wetlands").
- Samples at the Hawks Prairie Reclaimed Water Basin 4 were collected monthly from January-October, 2018. Infiltration of Class A Reclaimed Water has occurred at this basin since 2006. Only samples collected during January, April, June, and August were analyzed for residual chemicals and PFAS.

Samples of vadose zone porewater were collected monthly from January-October, 2018 from the west and east halves of the Hawks Prairie Reclaimed Water Basin 4 (HDR, 2017c). Samples collected during January, April, June, and August were analyzed for residual chemicals and PFAS.

In addition, samples of effluent water, groundwater, and surface water were collected and analyzed for residual chemicals and other parameters of interest (HDR, 2017a, b, c).

Samples of effluent water were collected in November 2014 and February and August 2015 from the BIRWP (HDR, 2017c). Analyses were for residual chemicals and other water quality indicators but did not include PFAS.

Samples of groundwater were collected in 2013, 2015, 2016, and 2018 from domestic and municipal water wells and monitoring wells, to characterize groundwater quality across a wide geography and in both shallow and deep aquifers (HDR, 2017a). Samples were collected in the following two study areas:

- The Hawks Prairie Study Area, located in the vicinity of north Lacey—Samples were collected from residential wells, public supply wells, monitoring wells, and springs. Samples

were collected in November 2013 (MW-1, -2, -3, -6, -8, -10, and -11 only) and from April to September 2015 from 20 residential wells, 12 public supply wells, one monitoring well (Thurston County well MW-1), and two springs (the Salmon Lane-area springs and the Beatty Spring)). Resampling was also conducted at three of the Hawks Prairie wells (residential well RES-983 and the City of Lacey wells S-16 (MUN-1217) and S-31) on May 2, 2016 because of errors in the original sample collection and laboratory mislabeling of sample bottles, as well as at MW-7 on November 15, 2016. Additional groundwater samples were collected monthly from January-October 2018 at 14 monitoring wells (only samples collected during January, April, June, and August 2018 were analyzed for residual chemicals and PFAS).

- The Tumwater Study Area, located in the vicinity of Tumwater—While reclaimed water has never been used for infiltration to groundwater within this study area, it is used for irrigation at several sites, and LOTT may develop an infiltration site in this area in the future. Samples were collected from 20 residential wells and 10 public supply wells. Samples were collected from August to September 2015.

Both the Hawks Prairie Study Area and the Tumwater Study Area are characterized as having residential and rural-residential land uses, with moderate commercial activity. Drinking water comes from groundwater, provided to some residents by public supply wells and to others by individual residential wells.

Samples of surface water were collected from August - December 2015 from the Deschutes River and Woodland Creek and their tributaries (HDR, 2017b), as follows:

- Deschutes River water—Sampling was conducted at six locations, including Upper Deschutes River (River Mile (RM) 4.8, Lower Deschutes River (RM 0.5), and tributary monitoring locations on Chambers Creek, Munn Lake, and Percival Creek, as well as one reference location on the Deschutes River (RM 9.4).
- Woodland Creek watershed—Sampling was conducted at six locations, including Upper Woodland Creek RM) 3.4), Lower Woodland Creek (RM 1.6), and tributary monitoring locations on Fox Creek, Beatty Springs, and Eagle Creek, as well as one reference location on Woodland Creek (RM 5.2).

Surface water samples were collected at various times of the year to assess variability under different flow conditions: two samples during late summer low flow conditions, one sample after the first large fall storm, and one sample during winter high flow conditions. Analyses were for residual chemicals and other water quality indicators but did not include PFAS or some other compounds (e.g., 1,4-dioxane, NDMA, salicylic acid, theophylline; see Table A-1).

2.2 Evaluation of Relevant Datasets and Identification of Chemicals of Interest

Water samples collected in Tasks 1 and 2 of the RWIS were analyzed for a range of water quality parameters regulated in drinking water and wastewater and for 122 unregulated chemicals (including 109 “residual chemicals” found in household products, pharmaceuticals, and personal care products, and 13 PFAS). These chemicals were selected for analysis because they have been reported at very low concentrations (on the order of parts per trillion (ppt), or nanograms per liter (ng/L)) in previous

studies of treated wastewater, groundwater, and surface water, and were selected from among the thousands of commonly used compounds of this type to include compounds that are:

- Representative of large classes of compounds,
- Frequently detected in reclaimed water,
- Routinely used in the wastewater industry for evaluating treatment effectiveness, and
- Reliably quantified in laboratory analysis.

All chemicals within the residual chemical and PFAS chemical groups that were analyzed for in reclaimed water or porewater in the sampling programs described in Section 2.1 were considered in the screening-level evaluation.

Reclaimed water and porewater data sets compiled by HDR and input into the project database were queried for use in the screening-level evaluation (HDR, 2017a, b, c). Data were reviewed for quality by HDR prior to delivery to Intertox. Any sample result that had an "R" qualifier (indicating a rejected result) was not included in the screening-level evaluation. If an analyte was not detected in any sample of reclaimed water or porewater, it was not included in the screening-level evaluation. If an analyte was detected in one or more samples, the highest detected concentration was used. Data for other media (effluent water, groundwater, surface water; HDR, 2017a, b, c) were reviewed and summarized for comparison to reclaimed water and porewater; these results are summarized in Appendix A.

Overall, 27 reclaimed water and 24 porewater samples were included in the assessment (Table 2-1). A total of 76 residual chemicals and 7 PFAS were detected in at least one sample—these chemicals were included as COIs in the screening-level evaluation. Chemicals identified as COIs, and their maximum-detected concentrations in reclaimed water and porewater, are listed in Table 2-2 for residual chemicals and in Table 2-3 for PFAS.

2.3 Chemicals of Interest Selection Uncertainties

Except for hormones and PFAS (see Section 5.0), if a chemical was never detected in either reclaimed water or porewater, it was not included as a COI in the screening-level evaluation and risk-based concentrations were not identified for the compound. It is possible that detection limits for some never-detected chemicals could exceed health risk-based acceptable concentrations in drinking water (i.e., DWELs derived per the methodology described in Section 4.0). Compounds that were analyzed for but never detected in either reclaimed water or porewater, and their detection limits, are listed in Table 2-4. However, as shown, detection limits of residual chemicals and PFAS in reclaimed water or porewater are quite low (≤100 ng/L). By comparison, most DWELs established for COIs (discussed in Section 4.0) are higher (with the exception of some hormones, which were all recommended for inclusion for further evaluation in the HHRA regardless of detection status, as discussed in Section 5.0). This suggests it is unlikely that a nondetected compound could be present at a level associated with a significant health risk. In addition, as discussed in Section 4.0, the derived DWELs incorporate multiple conservative assumptions and safety factors, such that levels

that would be associated with actual health risk are much higher. The potential for underestimating risks for chemicals not detected above the analytical detection limits used in this project is thus assumed to be minimal.

Table 2-1. Summary of Results of Analyses for Residual Chemicals and PFAS in Reclaimed Water and Porewater

Chemical	Number of Samples	Number of Chemicals Analyzed		Number of Chemicals Detected	
		Residual Chemicals	PFAS	Residual Chemicals	PFAS
Reclaimed Water	27	109	13	73	5
Porewater	24	100	13	55	7
Overall Total	**51**	**109**	**13**	**76**	**7**

Table 2-2. Residual Chemicals Detected in Reclaimed Water and Porewater Identified as Chemicals of Interest (COIs), with Maximum-Detected Concentrations

Chemical	Category or Pharmaceutical Class	Maximum-Detected Conc. (ng/L)*	
		Reclaimed Water	Porewater
1,4-Dioxane	Industrial chemical	850	750
1,7-Dimethylxanthine	Caffeine degradate	36	45
2,4-D	Herbicide	160	20
4-Nonylphenol	Surfactant	3,100	510,000
4-para-Nonylphenol	Surfactant	240	NA
4-tert-Octylphenol	Surfactant	130	<50
Acesulfame-K	Sugar substitute	13,000	1,000
Acetaminophen	Analgesic	160	39
Albuterol	Anti-asthmatic	11	8.0
Amoxicillin	Antibiotic	33	<20-<80
Atenolol	Beta blocker	230	130
Azithromycin	Antibiotic	<20	NA
Bisphenol A	Plasticizer	<100	28
Bromacil	Herbicide	14	<5
Butalbital	Analgesic	51	54
Caffeine	Stimulant	76	38
Carbadox	Antibiotic	14	<5
Carbamazepine	Antiseizure	730	850
Carisoprodol	Muscle relaxant	110	35
Chloramphenicol	Antibiotic	24	<10-<50
Chloridazon	Enzyme	9	62
Clofibric Acid	Cholesterol drug/ Herbicide	120	30
Cotinine	Nicotine degradate	130	25
Cyanazine	Triazine herbicide	9	<5
Diaminochlorotriazine (DACT)	Triazine herbicide	12	<5-<50
Desethylatrazine (DEA)	Triazine herbicide	20	<5-<25
N,N-Diethyl-meta-toluamide (DEET)	Mosquito repellant	140	500
Dehydronifedipine	Blood pressure drug metabolite	8.7	5.7
Diazepam	Antianxiety	9.3	<5
Diclofenac	Anti-inflammatory	260	81
Dilantin	Anti-seizure	130	82
Diltiazem	Calcium blocker	370	5.3
Diuron	Herbicide	100	90
Erythromycin	Antibiotic	25	48
Estradiol	Estrogenic hormone	<5-<25	35
Estrone	Estrogenic hormone	1.9	<5-<25
Ethinyl estradiol - 17 alpha	Contraceptive hormone	64	49
Flumequine	Antibiotic	98	54
Fluoxetine	Antidepressant	210	<10

Chemical	Category or Pharmaceutical Class	Maximum-Detected Conc. (ng/L)* Reclaimed Water	Porewater
Gemfibrozil	Antilipidemic	710	30
Ibuprofen	Analgesic	320	12
Iohexal	X-ray contrast agent	14,000	2,200
Iopromide	X-ray contrast agent	540	37
Ketorolac	Anti-inflammatory	18	5.3
Lidocaine	Anesthetic	550	320
Lincomycin	Antibiotic	76	65
Linuron	Herbicide	6.9	7.9
Lopressor	Beta blocker	900	510
Meclofenamic acid	Anti-inflammatory	300	130
Meprobamate	Anti-anxiety	390	57
Metformin	Antidiabetic	2,600	11
Methylparaben	Preservative	21	48
Naproxen	Analgesic	32	<10-<50
Nifedipine	Calcium blocker	20	<20-<100
N-Nitroso dimethylamine (NDMA)	Industrial solvent	7.3	8.2
Norethisterone	Steroid hormone	5.9	5.0
OUST (Sulfometuron methyl)	Herbicide	11	<5
Oxolinic acid	Antibiotic	64	<10
Pentoxifylline	Blood thinner	10	<5
Primidone	Anti-convulsant	930	330
Quinoline	Industrial chemical	28	<5
Salicylic Acid	Keratolytic agent	130	<100-<500
Simazine	Triazine herbicide	7.7	<5
Sucralose	Sugar substitute	90,000	470,000
Sulfadiazine	Sulfa antibiotic	14	300
Sulfadimethoxine	Sulfa antibiotic	17	39
Sulfamethoxazole	Sulfa antibiotic	520	700
Tris(2-carboxyethyl)phosphine (TCEP)	Flame retardant	240	240
Tris(1-chloro-2-propyl) phosphate (TCPP)	Flame retardant	1,300	1,200
Tris(1,3-dichloroisopropyl)phosphate (TDCPP)	Flame retardant	2,000	1,300
Testosterone	Steroid hormone	7.4	31
Theobromine	Caffeine degradate	66	490
Theophylline	Anti-asthmatic	120	160
Thiabendazole	Fungicide	600	9.1
Triclosan	Antimicrobial	130	130
Trimethoprim	Antibiotic	97	17

*For compounds never detected in a medium, the detection limit or range of detection limits is given (<).
NA – Not analyzed

Table 2-3. PFAS Compounds Detected in Reclaimed Water and Porewater Identified as Chemicals of Interest (COIs), with Maximum-Detected Concentrations

Chemical	Category or Pharmaceutical Class	Maximum-Detected Conc. (ng/L)	
		Reclaimed Water	Porewater
Perfluoro butanoic acid (PFBA)	PFAS	<10	17
Perfluoro octanoic acid (PFOA)	PFAS	22	31
Perfluoro-1-butanesulfonate	PFAS	13	27
Perfluoro-1-butanesulfonic acid	PFAS	13	26
Perfluoro-n-hexanoic acid	PFAS	81	80
Perfluoro-n-nonanoic acid	PFAS	<5	5.7
Perfluoropentanoic acid	PFAS	150	120

*For compounds never detected in a medium, the detection limit or range of detection limits is given (<).

Table 2-4. Residual Chemicals and PFAS Never Detected in Reclaimed Water or Porewater and Their Limits of Detection

Chemical	Category or Pharmaceutical Class	Limit(s) of Detection (ng/L)
4-n-Octylphenol diethoxylate	Surfactant	100
4-n-Octylphenol monoethoxylate	Surfactant	100
Androstenedione	Hormone	5-10
Atrazine	Triazine herbicide	5
Azithromycin	Antibiotic	20
Bendroflumethiazide	Triazide	5-25
Bezafibrate	Lipid regulator	5
Butylparaben	Preservative	5-25
Chlorotoluron	Herbicide	5
Cimetidine	H2 blocker	5
Deisopropylatrazine (DIA)	Triazine degradate	5-25
Estradiol - 17 beta	Hormone	0.5-5
Estriol	Hormone	10-50
Ethylparaben	Preservative	20-100
Isobutylparaben	Preservative	5-25
Isoproturon	Herbicide	100
Ketoprofen	Anti-inflammatory	5
Metazachlor	Herbicide	5
Metolachlor	Herbicide	5
Nonylphenol diethoxylate	Antioxidant	100
Nonylphenol monoethoxylate	Antioxidant	100
Octylphenol	Antioxidant	100
Phenazone	Analgesic	5
Progesterone	Hormone	5
Propazine	Triazine herbicide	5
Propylparaben	Preservative	5-25
Sulfachloropyridazine	Sulfa antibiotic	5
Sulfamerazine	Sulfa antibiotic	5-25
Sulfamethazine	Sulfa antibiotic	5
Sulfamethizole	Sulfa antibiotic	5
Sulfathiazole	Sulfa antibiotic	5-20
Triclocarban	Antibacterial	5-10
Warfarin	Anticoagulant	5
Perfluoro octanesulfonate (PFOS)	PFAS	5
Perfluoro octanesulfonic acid (PFOS)	PFAS	5
Perfluoro-1-hexanesulfonate	PFAS	5
Perfluoro-1-hexanesulfonic acid	PFAS	5
Perfluoro-n-decanoic acid	PFAS	5
Perfluoro-n-heptanoic acid	PFAS	5

3.0 EXPOSURE ASSESSMENT

The goal of the Exposure Assessment is to identify EPCs for use in the screening-level evaluation. The identification of EPCs is summarized below

3.1 Identification of EPCs

For purposes of this screening step, the EPC for each COI is assumed to be the maximum concentration measured in reclaimed water or porewater at any sampling location, as determined from the Task 1 and 2 sampling.

Maximum-detected concentrations of COIs in these media are summarized in Tables 2-2 and 2-3 for residual chemicals and PFAS, respectively.

3.2 Exposure Assessment Uncertainties

This screening-level evaluation is conducted using conservative assumptions about the concentrations to which people could be exposed. Specifically, the assessment assumes exposure to the maximum-detected concentration of each COI detected in reclaimed water or porewater on a daily basis over an extended period of time (i.e., chronically) for noncarcinogens or for a lifetime for carcinogens. Repeated, daily exposure to concentrations of this magnitude from reclaimed water is unlikely. Even if exposure did occur, average exposure concentrations would be lower. Further, direct and repeated exposure to reclaimed water or porewater as a drinking water source is unlikely. Given application of these conservative assumptions, if compounds are not detected in reclaimed water or porewater at concentrations in excess of DWELs, significant human health risks from exposure to these compounds in reclaimed water is unlikely. The HHRA will more closely investigate potential exposure scenarios and derive more realistic estimates of human exposure and potential health risk.

4.0 TOXICITY ASSESSMENT

The goal of the Toxicity Assessment step is to identify risk-based decision guides (i.e., ADIs) for each COI as well as corresponding DWELs assuming a conservative (health-protective) estimate of the average daily drinking water ingestion rate. These DWELs will be compared to the maximum-detected concentrations in reclaimed water and porewater in Section 5.0.

The following sections describe the process for identifying ADIs for the COIs and summarize the corresponding DWELs.

4.1 The Dose-Response Concept

Detection of a chemical in water does not mean that adverse health effects will occur or are likely. While all chemicals are potentially toxic at some dose, many factors play a role in whether or not a chemical is toxic or harmful to humans or animals. In particular, the dose, or amount, of chemical a person or animal receives is important in determining the likelihood that a chemical will cause an adverse effect.

While some chemicals are toxic in very small amounts, others are only toxic when the exposure is very large. The duration, or how long, a person is exposed is also important: exposure to some substances over a short period of time (known as acute exposure) may not be harmful while exposure over many years (known as chronic exposure) can cause adverse health effects.

The nature of toxicological effects from exposure to different substances varies depending on how they act in the body, with effects potentially ranging from cancer to noncarcinogenic effects such as effects on reproductive capacity, growth and development, immune parameters, and organ systems. To predict the potential for a given substance to cause toxicity, scientists conduct tests in animals or evaluate humans that have been unintentionally or intentionally exposed (e.g., to medications). Newer methods using computer models can also predict toxicity. With this information, scientists can determine the dose at which adverse effects can occur and the nature of the response (i.e., the "dose-response"). They can also estimate the likelihood that exposure at a given dose will have a harmful effect in humans. This process is referred to as "risk assessment."

To determine whether detected concentrations of COIs could present a significant health risk to people who consume the water, the availability of existing ADIs or corresponding DWELs, such as U.S. EPA Maximum Contaminant Levels (MCLs), was determined. If an appropriate existing value was not available, screening-level human health risk-based ADIs and DWELs were derived from published toxicity data and therapeutic dosing information, following a decision tree approach.

DWELs in ng/L (equivalent to a part per trillion or ppt) were derived from existing toxicity criteria or calculated ADIs (in units of µg/kg body weight-d) by dividing the ADI by a daily drinking water consumption rate corresponding to a 10 kg child (1 L/day, or 0.1 L/kg-d; U.S. EPA, 2018) and multiplying by a conversion factor (1,000 ng/µg), as follows:

$$DWEL\ (ng/L)\ =\ \frac{ADI\ (\mu g/kg-d)\ \times\ 10\ kg}{1\ L/d} \times \frac{1000\ ng}{\mu g}$$

This daily drinking water consumption rate (0.1 L/kg-d) is recommended by U.S. EPA (2018) for use in deriving one-day and 10-day health advisories for drinking water, and is more health protective than values based on adult body weight and adult water consumption. As described by U.S. EPA (2019), water ingestion per unit of body weight decreases with increasing age. For example, the average drinking water ingestion rate for adults (age 21 to <50 years) is 0.016 L/kg-d, and the 95th percentile is 0.044 L/kg-d. Consequently, it is assumed that use of a drinking water consumption rate of 1 L/kg-d is protective of all members of the population.

The process used to identify MCLs or ADIs, and to derive DWELs, is described below.

4.2 Process for Identifying ADIs

For each of the detected chemicals, an ADI was selected or derived per a decision tree approach (Figure 4.1). This decision tree is based on an approach developed in WateReuse Foundation Project #05-005, *Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Health Concern from Potential Presence in Water Intended for Indirect Potable Reuse* (Snyder et al., 2010), and elaborated upon in Water Research Foundation Project 4387, *Development of a Water Utility Primer on EDCs/PPCPs: Technical Summary* (Intertox, 2015). In WRF-05-005, methodologies for developing screening-level human health risk-based criteria for pharmaceuticals and personal care product ingredients (PPCPs) and endocrine disruption compounds (EDCs) potentially present in water intended for indirect potable reuse were reviewed by a panel of experts comprised of regulators, scientists, water professionals, and other interested parties. Decision criteria were then developed to help in the selection of an appropriate screening methodology that can be used to rapidly develop a screening-level for water in the event that a "new" chemical is detected.

Briefly, the approach is as follows:

1. The availability of existing MCLs or ADIs published by authoritative bodies and other entities was determined, and the value from among these that resulted in the lowest DWEL was selected for further consideration. To establish whether the value reflects current understanding of the chemical's toxicology, it was then examined more closely (e.g., When was it established and by whom? What data were considered in its derivation? Was the established value derived using standard and accepted risk assessment methodologies? Was it peer-reviewed?) Chemicals with "dated" values or values derived using non-standard methods or not subject to peer-review, as well as any pharmaceutical compounds, were evaluated further and additional "comparison levels" established per the methods described below. Otherwise, the identified ADI was applied to the chemical.
2. For compounds detected in drinking water without identified published MCLs or ADIs or other screening-levels that were determined to be of sufficient quality for application to the chemical, and for all pharmaceutical compounds, comparison levels were derived from published toxicity data and other information using several methodologies per a decision tree approach (Figure 4.1). The lowest of these comparison levels was selected as the ADI.

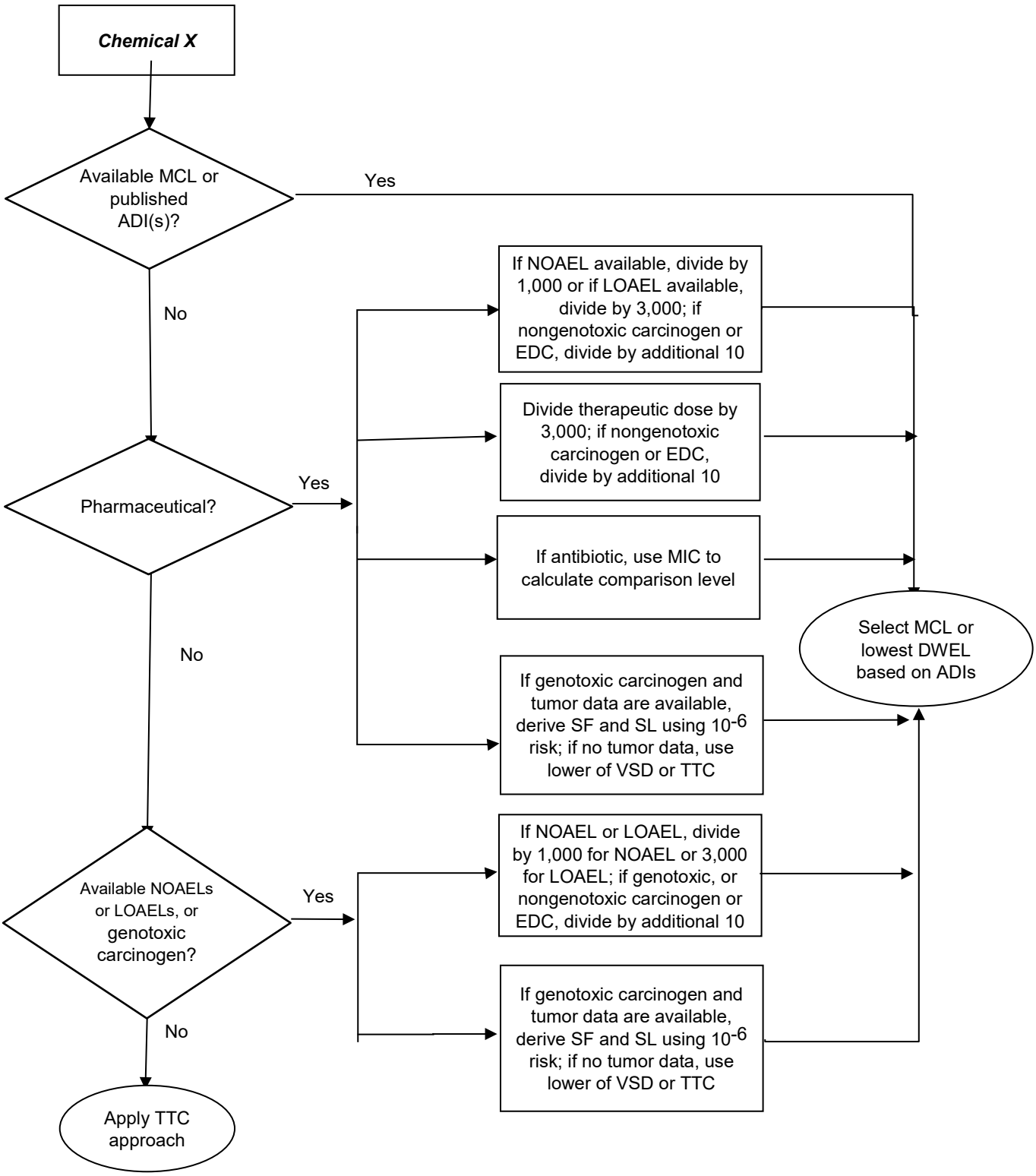

Figure 4-1. Decision Tree for Identifying ADIs for Chemicals of Interest

The process for selection or derivation of an ADI for each COI is described in more detail below.

4.2.1 Identification of Existing MCLs or ADIs

For each of the compounds, the availability of existing MCLs or ADIs published by authoritative bodies and other entities was determined. Sources of values considered include the following:

- U.S. EPA Safe Drinking Water Act (SDWA) National Primary Drinking Water Regulations MCL
- Washington State Department of Health Maximum Contaminant Levels (MCLs) for drinking water
- U.S. EPA Reference Doses (RfDs) for noncancer effects
- U.S. EPA oral Slope Factors (SFs) for cancer
- U.S. EPA Unregulated Contaminant Monitoring Rule (UCMR) Contaminant Candidate List (CCL) Health Reference Levels (HRLs)
- U.S. EPA Regional Screening-levels (RSLs)
- U.S. EPA Drinking Water Health Advisories (HAs)
- ATSDR Minimal Risk Levels (MRLs) for noncancer effects, for intermediate and chronic duration exposures
- Washington State Water Quality Standards for Ground Waters– Chapter 173-200 WAC
- Washington State Model Toxics Control Act (MTCA) Groundwater Cleanup Standards (Chapter 173-340 WAC, Method B and C)
- California EPA Public Health Goals (PHGs) for drinking water
- California EPA No Significant Risk Levels (NSRLs) for cancer and reproductive/ developmental toxicity developed as part of the Proposition 65 program
- California EPA oral SFs for cancer
- Minnesota Department of Health (MDH) Human Health-Based Values (HBVs) or noncancer Human Risk Limits (nHRL) for drinking water
- European Food Safety Authority (EFSA) ADIs
- Joint FAO/WHO Expert Committee on Food Additives (JEFCA) ADIs
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR) ADIs
- Other sources of values as appropriate

ADIs for noncancer endpoints are presented in units of micrograms per kilogram of body weight per day (µg/kg-d). For cancer endpoints, published SFs (presented in units of the proportion of a population affected per milligram of exposure per kilogram of body weight per day ($(mg/kg\text{-}d)^{-1}$)) were converted to ADIs in units of µg/kg-d by assuming an acceptable lifetime excess cancer risk (*de minimis* risk) of 1 in one million (10^{-6}) and that a person is exposed to the chemical at this dose daily over a lifetime (U.S. EPA 2005a), and multiplying by a conversion factor (1000 µg/mg). Per U.S. EPA (2005a), a slope factor is an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to a substance.

Specifically, comparison levels for cancer were derived from published SFs as follows:

$$Comparison\ level_{CSF}\ (\mu g/kg-d) = \frac{10^{-6}}{SF\ (mg/kg-d)^{-1}} \times 1000\ \mu g/mg$$

If an ADI was presented as a dose (e.g., in units of µg/kg-d), it was converted to a DWEL assuming a 10 kg child consumes 1 L/day, or 0.1 L/kg-d (U.S. EPA, 2018), as follows:

$$DWEL\ (\mu g/L)\ = \frac{ADI\ (\mu g/kg-d)\ \times\ 10\ kg}{1\ L/d}$$

The value from among these that resulted in the lowest DWEL was selected for further consideration.

All tentatively selected DWELs based on existing ADIs were examined more closely to confirm that the selected value reflects current understanding of the toxicology/ health risk of exposure to the chemical and is appropriately health protective. For example, questions considered were: When was the value established and by whom? What data were considered in its derivation? Was the value derived using standard and accepted risk assessment methodologies? Was it peer-reviewed? Chemicals having values that were "dated" or that were derived using non-standard methods or not subject to peer-review, as well as any pharmaceutical compounds, were evaluated further—for these chemicals, additional "comparison levels" were identified per the methods described below (Section 4.2.2) and outlined in the decision tree (Figure 4-1). Otherwise, the identified ADI was selected for application to the chemical.

Existing MCLs or ADIs identified for the COIs are presented in Appendix B, Table B-1.

4.2.2 Methods for Deriving Comparison Levels

Methods used to derive comparison levels per the decision tree approach are described in more detail below.

As discussed by the expert panel in WRF-05-005, making chemical-specific uncertainty factor decisions for a large number of compounds is a major endeavor, requiring careful resource-intensive weighing of the database and its various uncertainties, and can engender disagreement. As such, generic but conservative uncertainty factors were applied for each methodology, to simplify the process of developing conservative screening values for the screening-level evaluation.

4.2.2.1 Derivation of Comparison Levels Using NOAELs or LOAELs from Toxicity Studies

Comparison levels for noncancer endpoints were derived from data on no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELs) for noncancer effects reported in animal toxicity studies or studies in humans (e.g., clinical trials), if available.

When establishing guidelines or standards for noncarcinogenic effects, including RfDs (U.S. EPA, 2002a), MRLs (ATSDR, 2007), and tolerable daily intakes (TDIs) (WHO, 1994), agencies charged with developing guidance values typically identify some threshold level of exposure below which adverse health effects have not been observed and, based on review of toxicity data, identify a corresponding point of departure upon which to base the guidance level. This is typically the highest

dose at which an effect is not seen (the NOAEL) or the lowest dose at which an effect is seen (the LOAEL). Below this dose, there is no evidence in animals or humans of a statistically or biologically significant increase in adverse effects, although some changes may occur that are not considered adverse (e.g., changes in certain enzyme levels). This "point of departure" is then divided by uncertainty factors (UFs) to derive a screening value considered protective to broader population groups, including sensitive populations such as children or people with immune compromised systems, as follows:

$$Comparison\ level_{Noncancer}\ (\mu g/kg-d) = \frac{NOAEL\ or\ LOAEL\ (\mu g/kg-d)}{UFs}$$

Generally, several multiplicative UFs are applied, individually ranging in value from 3 to 10 with each factor representing a specific area of uncertainty in the available data (e.g., intraspecies uncertainty/ variability, interspecies uncertainty/ variability, extrapolation from a LOAEL to a NOAEL, extrapolation from less-than-lifetime exposure to lifetime exposure, and database uncertainties). When high quality toxicity data are available, combined uncertainty factors typically range from 30 to 1,000. Per U.S. EPA risk assessment guidance (U.S. EPA, 2008), a factor of 3 represents a "partial" uncertainty factor, equal to the half-log (square root) of 10 (i.e., $10^{1/2}$), usually rounded to 3 for use in risk assessment. As such, by convention, when two UFs with a value of 3 are multiplied together, the resulting combined UF is 10 (not 3 × 3 =9).

However, making chemical-specific UF decisions for a large number of compounds is a major endeavor, requiring careful resource-intensive weighing of the database and its various uncertainties, and can engender disagreement. To simplify the process of developing screening values, a more generic screening protocol was applied: applying a default cumulative UF of 1,000 when the point of departure is a NOAEL and a UF of 3,000 when the point of departure is a LOAEL, rather than deriving UFs on a study-specific basis. Application of default UFs of 1,000 and 3,000 is supported by a statistical analysis of a set of 216 "learning compounds" with U.S. EPA RfDs, NOAELs, and LOAELs conducted by U.S. EPA as part of the Contaminant Candidate List (CCL) Classification Process (U.S. EPA, 2012b).

An additional UF of 10 was also applied if the substance was determined to be either a nongenotoxic carcinogen, an EDC, or genotoxic but with negative or inconclusive evidence for carcinogenicity in the existing animal studies. If the substance was determined to have more than one of these characteristics (e.g., a nongenotoxic carcinogen and an EDC), only one factor of 10 was applied.

In a manner analogous to U.S. EPA RfDs, screening-levels derived using this approach are assumed to correspond to the amount of a chemical to which a person, including members of sensitive subpopulations, can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect (U.S. EPA, 1993). Study types of most relevance for evaluating long-term low-level exposures to compounds in water are assumed to be subchronic, chronic, reproduction, and developmental toxicity (teratology) studies with exposure primarily via the oral

route. The studies primarily assessed impacts on mice and rats, but could also include rabbits, dogs, primates, and other animals.

Comparison levels derived from noncancer toxicity endpoints for the COIs without a selected existing ADI of sufficient quality are presented in Appendix B, Table B-2.

4.2.2.2 Derivation of Comparison Levels Based on the Lowest Therapeutic Dose of Pharmaceuticals

The lower end of a drug's therapeutic range can be considered an estimate of the threshold for appreciable biological activity in target populations, and therefore may be considered a threshold for potential adverse effects. Following an approach analogous to the NOAEL/ LOAEL approach, for pharmaceutical compounds a comparison level was derived by dividing the lowest therapeutic dose by UFs to account for extrapolation from the LOAEL to a NOAEL, variations in susceptibility between different members of the population, or data gaps:

$$Comparison\ level_{LTD}\ (\mu g/kg-d) = \frac{Lowest\ Therapeutic\ Dose\ (\mu g/kg-d)}{UFs}$$

A composite uncertainty factor of 3,000 was used. This approach assumes that the lowest therapeutic dose is effectively equivalent to a LOAEL. An additional UF of 10 was also applied if the substance was determined to be either a nongenotoxic carcinogen, an EDC, or genotoxic but with negative or inconclusive evidence for carcinogenicity in the existing animal studies. If the substance was determined to have more than one of these characteristics (e.g., a nongenotoxic carcinogen and an EDC), only one factor of 10 was applied.

Comparison levels derived from therapeutic doses for pharmaceutical COIs are presented in Appendix B, Table B-3.

4.2.2.3 Derivation of Comparison Levels for Carcinogenicity Based on Tumor Incidence Data

For chemicals with positive evidence of genotoxicity in laboratory experiments and reported evidence of carcinogenicity in high dose animal studies, a linear extrapolation model was used to predict the tumorigenic response at low doses. These types of models assume a linear relationship between risk and dose at low doses (i.e., they assume the absence of a threshold below which there is no risk; U.S. EPA, 2005). These types of models are conservative (health-protective) and are applied when there is an absence of sufficient information on modes of action or when the mode of action information indicates the dose-response curve at low dose is expected to be linear. The slope of the risk/dose line, known as the slope factor (SF), is an upper-bound estimate of risk per increment of dose (e.g., per 1 mg/kg-day of exposure) that can be used to estimate risk probabilities for different exposure levels.

In this assessment, if sufficient data on tumor incidence per dose level were available for a given compound with evidence of carcinogenicity in animal bioassays, and data indicate that the compound is genotoxic and assumed to have a linear relationship between carcinogenicity and dose, a multi-

stage carcinogenicity model was used to estimate a SF. For these compounds, U.S. EPA's Benchmark Dose Software v.2.3 (BMDS 2.3) (U.S. EPA 2012a) was used to model the data in the observed range and estimate a benchmark dose level (BMDL) for a benchmark response of 10% extra risk, which is generally at the low end of the observable range for standard cancer bioassay data. This BMDL serves as the "point of departure" for linear extrapolation (U.S. EPA, 2002a).

Comparison levels were then calculated assuming an acceptable lifetime excess cancer risk of 1 in one million (10^{-6}) and that a person is exposed to the chemical at this dose daily over a lifetime (U.S. EPA, 2005a). Specifically, a comparison level was calculated as indicated in Section 4.2.1 above for cancer SFs.

In some cases, a chemical was reported to show evidence of carcinogenicity in animal studies, but no data on tumor incidence were located that could be used to develop a cancer SF. To be conservative and avoid dismissing a compound because of lack of data, if the compound is a nongenotoxic carcinogen and no tumor incidence data were identified, an additional UF of 10 was applied to the lowest therapeutic dose or the NOAEL/ LOAEL. If the compound is a genotoxic carcinogen and no tumor incidence data were identified, a comparison level was derived by dividing the maximum tolerated dose by 740,000 (the Gaylor and Gold 1998 VSD approach for genotoxic carcinogens, discussed below).

Evidence for carcinogenicity and genotoxicity and comparison levels derived from tumor incidence data for the COIs without existing published ADIs are presented in Appendix B, Table B-4. For purposes of this project, the genotoxicity assumptions applied to assess carcinogenicity potential were based on data identified for four several different *in vitro* genotoxicity test types, including the bacterial reverse mutagenicity assay in *Salmonella typhimurium* (Ames test) or in *E. coli*, the mouse lymphoma assay (MLA), or micronucleus assays or chromosomal aberration assays in mammalian cells. *In vivo* test results were also considered. Based on results from these tests, the determination of genotoxicity was made as follows:

- Compounds that tested negative in all tests for which data were available were assumed to be nongenotoxic (negative), and
- Compounds that tested positive in one or more tests for which data were available were assumed to be genotoxic (positive) unless data for multiple other assays of the same type reported negative results, or if an authoritative body (e.g., the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), or U.S. EPA) concluded that the compound was not genotoxic based on the weight of evidence and mechanistic considerations.

However, with regard to interpreting negative genotoxicity tests as indicative of noncarcinogenicity, it was noted that some compounds may be carcinogenic via nongenotoxic mechanisms (e.g., liver enzyme induction, peroxisome proliferation, hormonal carcinogens).

4.2.2.4 Derivation of a Virtually Safe Dose for Carcinogens

For compounds with evidence of carcinogenicity in animals and with evidence of genotoxicity, but for which no tumor incidence data were identified, a virtually safe dose (VSD) was calculated using the method of Gaylor and Gold (1995).

Gaylor and Gold (1995) proposed a method for calculating a VSD without the need to conduct multi-year laboratory studies for carcinogenicity. Gold et al. created the Carcinogenic Potency Database summarizing results from 6,540 chronic, long-term animal cancer tests on 1,547 chemicals, as published in the general literature through 2001 and by the National Cancer Institute (NCI) or the National Toxicology Program (NTP) through 2004 (Gold et al., 2011). Gaylor and Gold (1995) reviewed the results of two-year cancer bioassays for 139 chemicals tested by the NTP and determined that a "virtually safe dose" corresponding to a cancer risk of 1 in a million can be estimated by dividing a chemical's maximum tolerated dose from 90-day studies in rodents by 740,000. The maximum tolerated dose is the highest dose predicted to produce minimal systemic toxicity over the course of a carcinogenicity study, estimated from 90-day dose range finding studies, and in practice is usually the high dose selected for a carcinogenicity study (FDA, 2005).

Comparison levels derived from VSDs without existing published ADIs that have evidence of carcinogenicity in animals and evidence of genotoxicity, but for which no tumor incidence data were identified as summarized in Appendix B, Table B-4, are presented in Appendix B, Table B-5.

4.2.2.5 Derivation of Comparison Levels for Antibiotics Based on Minimum Inhibitory Concentrations

Comparison levels for antibiotics were developed based on the minimum inhibitory concentration (MIC) to human gastrointestinal flora, defined as the lowest concentration of the antibiotic that will inhibit the visible growth of the microorganism (WHO, 1997; EMEA, 1998; Schwab et al., 2005; WHO, 2006). Comparison levels were developed from MICs using the following equation (WHO, 1997; 2006):

$$Comparison\ level_{MIC}\ (\mu g/kg-d) = \frac{MIC_{50}\ (mg/g) \times MCC\ (g/d) \times 1{,}000\ \mu g/g}{FA\ \times SaF\ \times BW\ (kg)}$$

Where:

MIC_{50}	=	Minimum inhibitory concentration of 50% of strains of the most sensitive relevant organism (mg/g, equivalent to µg/mL) [WHO (1997, 2006) is clear that the MIC_{50}, as opposed to the MIC, should be applied in the calculation]
MCC	=	Mass of colonic contents (g/day)
FA	=	Fraction of the dose available to the gastrointestinal microflora
SaF	=	Safety factor, with a magnitude depending on the quality and quantity of the microbiological data available
BW	=	Body weight (kg)

To develop comparison levels for antibiotics, the MIC for the most sensitive bacterial strain determined in susceptibility assays was selected; these values are available from KnowledgeBase (2020) for most of the study antibiotics. Fraction available (FA) was determined from the results of human clinical studies, or assumed to be 50% when no data were available. The mass of colonic contents (MCC) was assumed to be 220 g/day, as estimated by WHO (1997), and the assumed body weight (BW) of 80 kg was selected based on U.S. EPA's default body weight for adults. A safety factor (SaF) of 10 was applied to account for limitations in the database.

Comparison levels derived using the MIC approach for antibiotic pharmaceutical COIs are presented in Appendix B, Table B-6.

4.2.2.6 Derivation of Comparison Levels Based on Thresholds of Toxicologic Concern

For compounds without comparison levels derived using other approaches, a threshold of toxicologic concern (TTC) can be identified. The TTC approach assigns an exposure level (or concentration) that is thought very unlikely to produce an adverse effect from exposure to a given compound, based on an assessment of the body of toxicological data for structurally and chemically similar compounds. The concept was originally developed for food additives (Cheeseman et al., 1999; Kroes et al., 2004) and has been expanded to consider ingredients of pharmaceuticals (Dolan et al., 2005) and personal and household care products (Blackburn et al., 2005). The stated goal of application of TTCs is to help focus research efforts on those chemicals likely to pose the greatest toxicologic risk. In general, TTCs are considered best applied to compounds for which very limited or no toxicity data are available to conduct a traditional toxicity assessment (Kroes et al., 2004; Dolan et al., 2005).

Several TTC schemes have been developed, and all rely on assumptions about a chemical's activity based on chemical structure. Cramer et al. (1978) defined three chemical classes to which compounds can be assigned according to the presence of structural groups and other features based on a decision tree approach. The former European Chemicals Bureau provides open source software (ToxTree) that was used to assign chemicals of interest to a Cramer class based upon the compound's SMILES (simplified molecular input line entry specification) code. The software is currently available at the SourceForge website (http://toxtree.sourceforge.net /).

Two of the most popular schemes are Cheeseman et al. (1999) and Kroes et al. (2004). Cheeseman et al. (1999) extracted data on 709 carcinogens from the Gold carcinogenic potency database to examine the utility of using short-term toxicity data, the results of genotoxicity testing, and structural alerts to identify more and less potent subsets of compounds in the dataset. Kroes et al. (2004) further refined the structural groups identified by Cheeseman et al. (1999).

TTCs are generally expressed as an intake (e.g., in micrograms per person/day). These levels can be converted to comparison levels (in units of µg/kg-d) based on an assumed adult body weight (e.g., 80 kg) as follows:

$$Comparison\ level_{TTC}\ (\mu g/kg-d) = \frac{TTC\ (\mu g/d)}{BW\ (80\ kg)}$$

When applying TTCs, it is important that they only be applied to compounds that are structurally similar to those upon which the TTCs are based. Several authors have reviewed the application of TTCs to specific compound types. While TTCs have in general been developed using data for industrial compounds, Blackburn et al. (2005) evaluated the appropriateness of use of the TTCs determined by Munro et al. (1996) for evaluating ingredients of personal and household care products, by assigning 43 chemicals used in household and personal care products to the three Cramer classes, and comparing the range of no observed effect levels (NOELs) for those compounds to the range of NOELs used by Munro et al. (1996) to develop the TTCs. The results showed that the distribution of NOELs for household and personal care product ingredients fell well within the range of the NOELs for the larger database analyzed by Munro et al. (1996) (i.e., that the Munro et al. (1996) database is appropriately representative of the range of NOELs seen for the smaller subset), and that the published TTC values for the three Cramer classes appear to be adequately protective benchmarks (Munro et al., 1996).

Of note, the application of TTCs to pharmaceuticals is largely hypothetical; none of the TTC schemes explicitly considered deliberately biologically active compounds such as pharmaceuticals in their derivation. As such, the appropriateness of application of the TTCs to pharmaceuticals is uncertain. Furthermore, both Cheeseman et al. (1999) and Kroes et al. (2004) caution against applying TTCs to EDCs. However, since Munro et al. (1996) determined that TTC schemes are protective of a broader range of compound types than industrial compounds, and since one of the goals of this project is to derive a screening-level for each compound to aid utilities in decision making, TTCs were derived for all pharmaceuticals for comparison purposes and for EDCs when no other data was available.

4.2.2.7 Conversion of the Lowest Comparison Level to a DWEL

The lowest (most health-protective) identified comparison level for each compound was selected as the ADI for each COI. This ADI was then converted to a DWEL assuming a 10 kg child consumes 1 L/day, or 0.1 L/kg-d (U.S. EPA, 2018), as follows:

$$DWEL\ (\mu g/L)\ = \frac{ADI\ (\mu g/kg-d)\ \times\ 10\ kg}{1\ L/d}$$

A DWEL is similar to a maximum contaminant level goal (MCLG), which is calculated by U.S. EPA based on health data using similar approaches, to represent a concentration that is not likely to be associated with adverse health effects. A maximum contaminant level (MCL) is an enforceable level based on the MCLG that also takes other considerations into account, such as economic feasibility.

It was assumed that the ADIs and DWELs that are developed using this approach are conservative, in part because of the multiplicative conservative UFs that were determined by the WRF-05-005 expert

panel to be health-protective without the need to apply resource intensive investigation of the mechanism of action and toxicity of each compound.

4.3 Summary of Identified DWELs

Table 4-1 summarizes the DWELs identified using the decision tree approach for the COIs. Comparison levels and corresponding DWELs derived using each of the methodologies are summarized in Appendix B, Table B-7.

4.4 Toxicity Assessment Uncertainties

The risk-based concentrations identified and applied in this screening-level evaluation are intended to be health protective and thus are likely to overestimate potential risks from exposure to these chemicals. In particular, the ADIs and DWELs calculated using the approaches applied here are screening levels and do not reflect concentrations at or above which adverse effects are expected or likely. For example, they are set using very conservative (health protective) assumptions incorporating multiple uncertainty factors (ranging from 1,000 to 3,000 for most compounds, with additional factors of 10 applied for compounds with suggestion of genotoxicity, nongenotoxic carcinogenicity, or endocrine disrupting potential). While the DWELs assume exposure via only one exposure pathway (consumption of drinking water), they assume chronic (i.e., lifetime) daily exposure to the chemicals in drinking water at an intake rate assumed to be health-protective for the entire population. Thus, the exposure assumptions likely greatly overestimate potential exposures.

Overall, because of the multiple conservative assumptions incorporated into this assessment, if the concentration of a substance found in water is below the screening level, then one can be confident that no health effects are likely. If the concentration is at or above its screening level, then more detailed evaluation of the toxicity and occurrence and exposure to the substance (including consideration of additional exposure pathways if appropriate) is recommended.

Table 4-1. Summary of Selected Screening-level DWELs for Chemicals of Interest and Basis of Values

Chemical	DWEL (ng/L)	Basis of Value
1,4-Dioxane	370	Existing value (California EPA cancer SF)
1,7-Dimethylxanthine	8,300	NOAEL/LOAEL
2,4-D	30,000	Existing value (MDH HRL)
4-Nonylphenol	20,000	Existing value (MDA HBV)
4-para-Nonylphenol	20,000	Existing value (MDA HBV)
4-tert-Octylphenol	100,000	Existing value (MDA HBV)
Acesulfame-K	120,000	NOAEL/LOAEL
Acetaminophen	2,700	Therapeutic dose
Albuterol	7.5	Therapeutic dose
Amoxicillin	31,000	Therapeutic dose
Atenolol	1,000	Therapeutic dose
Azithromycin	25,000	Therapeutic dose
BPA (Bisphenol A)	20,000	Existing value (MDH nHRL-chronic)
Bromacil	13,000	NOAEL/LOAEL
Butalbital	2,000	Therapeutic dose
Caffeine	20,000,000	Existing value (NTP CERHR)
Carbadox	33,000	NOAEL/LOAEL
Carbamazepine	330	Therapeutic dose
Carisoprodol	10,000	Therapeutic dose
Chloramphenicol	4.1	Therapeutic dose
Chloridazon	180,000	NOAEL/LOAEL
Clofibric acid	8,300	Therapeutic dose
Cotinine	800	NOAEL/LOAEL
Cyanazine	1,000	Existing value (MDA HBV)
Diaminochlorotriazine (DACT)	3,000	Existing value (U.S. EPA MCL)
Desethylatrazine (DEA)	3,000	Existing value (U.S. EPA MCL)
N,N-Diethyl-meta-toluamide (DEET)	200,000	Existing value (MDA HBV)
Dehydronifedipine	1,200	Therapeutic dose
Diazepam	83	Therapeutic dose
Diclofenac	830	NOAEL/LOAEL
Dilantin	1,200	Therapeutic dose
Diltiazem	5,000	Therapeutic dose
Diuron	20,000	Existing value (U.S. EPA RfD)
Erythromycin	100,000	Therapeutic dose
Estradiol	0.26	Existing value (California EPA cancer SF)
Estrone	0.058	Therapeutic dose
Ethinyl Estradiol - 17 alpha	0.083	Therapeutic dose
Flumequine	25,000	NOAEL/LOAEL

Chemical	DWEL (ng/L)	Basis of Value
Fluoxetine	960	NOAEL/LOAEL
Gemfibrozil	5,000	Therapeutic dose
Ibuprofen	8,300	Therapeutic dose
Iohexol	500,000	NOAEL/LOAEL
Iopromide	500,000	NOAEL/LOAEL
Ketorolac	1,600	Therapeutic dose
Lidocaine	10,000	Therapeutic dose
Lincomycin	33,000	Therapeutic dose
Linuron	1,000	Existing value (MDH HRL)
Lopressor	1,000	Therapeutic dose
Meclofenamic acid	30,000	NOAEL/LOAEL
Meprobamate	22,000	Therapeutic dose
Metformin	41,000	Therapeutic dose
Methylparaben	5,500,000	NOAEL/LOAEL
Naproxen	13,000	Therapeutic dose
Nifedipine	1,200	Therapeutic dose
N-Nitroso dimethylamine (NDMA)	0.86	Existing value (WA MTCA GW Cleanup level Method B)
Norethisterone	1.4	Therapeutic dose
OUST (Sulfometuron methyl)	300,000	NOAEL/LOAEL
Oxolinic acid	110,000	NOAEL/LOAEL
Pentoxifylline	3,300	Therapeutic dose
Primidone	410	Therapeutic dose
Quinoline	3.3	Existing value (U.S. EPA cancer SF)
Salicylic acid	13,000	Therapeutic dose
Simazine	730	Existing value (WA MTCA GW cleanup level Method B)
Sucralose	1,500,000	NOAEL/LOAEL
Sulfadiazine	41,000	Therapeutic dose
Sulfadimethoxine	1,600,000	NOAEL/LOAEL
Sulfamethoxazole	5,300	Therapeutic dose
Tris(2-carboxyethyl) phosphine (TCEP)	500	Existing value (U.S. EPA cancer SF)
Tris(1-chloro-2-propyl) phosphate (TCPP)	200,000	Existing value (U.S. EPA cancer RfD)
Tris(1,3-dichloroisopropyl) phosphate (TDCPP)	2,000	Existing value (California EPA NSRL)
Testosterone	200	Therapeutic dose
Theobromine	6,600	NOAEL/LOAEL
Theophylline	660	Therapeutic dose
Thiabendazole	1,300	VSD
Triclosan	2,300	NOAEL/LOAEL
Trimethoprim	2,600	Therapeutic dose

Chemical	DWEL (ng/L)	Basis of Value
Perfluoro butanoic acid- PFBA	7,000	Existing value (MDH HBV)
Perfluoro octanesulfonate-PFOS	15	Existing value (MDH HBV)
Perfluoro octanesulfonic acid - PFOS	30	Existing value (MDH HBV)
Perfluoro octanoic acid - PFOA	35	Existing value (MDH HBV)
Perfluoro-1-butanesulfonate	2,000	Existing value (MDH HBV)
Perfluoro-1-butanesulfonic acid	200,000	Existing value (U.S. EPA RfD)
Perfluoro-n-heptanoic acid	70	Existing value (U.S. EPA HA for PFOA + PFOS)
Perfluoro-n-hexanoic acid	70	Existing value (U.S. EPA HA for PFOA + PFOS)
Perfluoro-n-nonanoic acid	30	Existing value (ATSDR MRL)
Perfluoropentanoic acid	70	Existing value (U.S EPA HA for PFOA + PFOS)

HA – Health Advisory; HBV – Health Based Value; HRL – Health Risk Level; LOAEL – lowest observed adverse effect level; MCL – U.S. EPA Maximum Contaminant Level; MDH – Minnesota Department of Health; nHRL – Noncancer Health Risk Level; NOAEL – no observed adverse effect level; NSRL – No Significant Risk Level for California EPA for Proposition 65; OEHHA – Office of Environmental Health Hazard Assessment (of California EPA); RfD – reference dose from U.S. EPA; SF – cancer slope factor estimated by the U.S. EPA or California EPA; VSD – virtually safe dose; WA WQS – Washington State Water Quality Standards for Ground Waters (Chapter 173-200 WAC)

5.0 RISK CHARACTERIZATION

In the Risk Characterization section, the maximum-detected concentration of each COI is compared to its DWEL, to identify chemicals recommended for consideration for inclusion in the HHRA.

If the concentration of the chemical is at or above the screening-level determined with this methodology, then more detailed evaluation of the toxicity, occurrence, and exposure to the chemical is recommended; if the concentration of that chemical is below the screening-level, then the risk to public health is predicted to be below levels of concern and, unless other considerations suggest further consideration of the chemical is warranted, the presence of the chemical at detected concentrations does not alone warrant further risk evaluation.

The results of the screening-level evaluation are presented in Tables 5-1, and the chemicals at or above their screening-level DWELs are summarized in Table 5-2. Results are discussed below.

5.1 Compounds with Maximum-Detected Concentrations That Exceed Their DWELs

Compounds with maximum-detected concentrations that exceeded their DWELs were:

- Four pharmaceutical compounds:
  - Albuterol, an anti-asthmatic, which was detected above its therapeutic dose-based DWEL of 7.5 ng/L in reclaimed water (maximum concentration 11 ng/L) and porewater (maximum concentration 8.0 ng/L).
  - Carbamazepine, an antiseizure medication, which was detected above its therapeutic dose-based DWEL of 330 ng/L in reclaimed water (maximum concentration 730 ng/L) and porewater (maximum concentration 850 ng/L).
  - Chloramphenicol, an antibiotic, which was detected above its therapeutic dose-based DWEL of 4.1 ng/L in reclaimed water (maximum concentration 24 ng/L). While not detected in porewater, some of the laboratory detection limits for this medium exceeded the DWEL (detection limit up to 50 ng/L).
  - Primidone an anti-convulsant, which was detected above its therapeutic dose-based DWEL of 410 ng/L in reclaimed water (maximum concentration 930 ng/L).
- Four hormones:
  - Estradiol, which was detected above its California cancer slope factor-based DWEL of 0.26 ng/L in porewater (maximum concentration 35 ng/L). While not detected in reclaimed water, the laboratory detection limits for this medium exceeded the DWEL (detection limits 5 to 25 ng/L).
  - Estrone, which was detected above its therapeutic dose-based DWEL of 0.058 ng/L in reclaimed water (maximum concentration 1.9 ng/L). While not detected in porewater, the laboratory detection limits for this medium exceeded the DWEL (detection limits 5 to 25 ng/L).
  - Ethinyl estradiol-17 alpha, which was detected above its therapeutic dose-based DWEL of 0.083 ng/L in reclaimed water (maximum concentration 64 ng/L) and porewater (maximum concentration 49 ng/L).

  - Norethisterone, which was detected above its therapeutic dose-based DWEL of 1.4 ng/L in reclaimed water (maximum concentration 5.9 ng/L) and porewater (maximum concentration 5.0 ng/L).
- Two PFAS:
  - Perfluoro-n-hexanoic acid, which was detected above its U.S. EPA Health Advisory (for PFOA + PFOS)-based DWEL of 70 ng/L in reclaimed water (maximum concentration 81 ng/L) and porewater (maximum concentration 80 ng/L).
  - Perfluoropentanoic acid, which was detected above its U.S. EPA Health Advisory (for PFOA + PFOS)-based DWEL of 70 ng/L in reclaimed water (maximum concentration 150 ng/L) and porewater (maximum concentration 120 ng/L).
- Five additional compounds:
  - 1,4-Dioxane, an industrial chemical, which was detected above its California EPA cancer slope factor-based DWEL of 370 ng/L in reclaimed water (maximum concentration 850 ng/L) and porewater (maximum concentration 750 ng/L).
  - 4-Nonylphenol, a surfactant, which was detected above its Minnesota Department of Health (MDH) Health Based Value (HBV)-based DWEL of 20,000 ng/L in porewater (maximum concentration 510,000 ng/L).
  - N-Nitroso dimethylamine (NDMA), an industrial solvent, which was detected above its Washington State MTCA Groundwater Cleanup Level- Method B value of 0.86 ng/L in reclaimed water (maximum concentration 7.3 ng/L) and porewater (maximum concentration 8.2 ng/L).
  - Quinoline, an industrial chemical, which was detected above its U.S. EPA cancer slope factor-based DWEL of 3.3 ng/L in reclaimed water (maximum concentration 28 ng/L). While not detected in porewater, the laboratory detection limits for this medium exceeded the DWEL (detection limit 5 ng/L).
  - Tris(1,3-dichloroisopropyl) phosphate (TDCPP), a flame retardant, which was detected at its California Office of Environmental Health Hazard Assessment (OEHHA) Proposition 65 No Significant Risk Level (NSRL)-based DWEL of 2,000 ng/L in reclaimed water.

Of the 15 compounds detected in reclaimed water or porewater at or above their DWELs, 13 were detected at or above their DWELs in one or more samples in reclaimed water and 10 were in porewater.

As shown in Table 5-1, several of the COIs (chloramphenicol, estradiol, estrone) that were detected at least once above their DWELs also had detection limits that exceeded their DWELs (where compounds were never detected in a given water medium, the detection limit is given as "<"(detection limit))—thus, these compounds could be present in some samples at concentrations below their detection limits that are nonetheless in excess of their DWEL.

5.2 Recommendations for Inclusion of Compounds in the HHRA

All 15 compounds that exceeded their DWELs in reclaimed water or porewater in the screening-level evaluation are recommended for consideration in the HHRA.

This assessment does not explicitly consider the potential for cumulative exposure to multiple chemicals in the same medium (i.e., it does not sum potential doses to all chemicals). However, given that multiple (4) hormones and PFAS (2) were detected at concentrations above their DWELs, and that at least some compounds within these chemical groups may act on the same physiological endpoints or through the same mechanisms of action, consideration of all of the compounds analyzed for within these groups for inclusion in the HHRA is recommended. This would include the following additional five hormones and 11 PFAS:

- Androstenedione
- Estradiol-17 beta
- Estriol
- Progesterone
- Testosterone
- Perfluoro butanoic acid (PFBA)
- Perfluoro octanesulfonate (PFOS)
- Perfluoro octanesulfonic acid
- Perfluoro octanoic acid (PFOA)
- Perfluoro-1-butanesulfonate
- Perfluoro-1-butanesulfonic acid
- Perfluoro-1-hexanesulfonate
- Perfluoro-1-hexanesulfonic acid
- Perfluoro-n-decanoic acid
- Perfluoro-n-heptanoic acid
- Perfluoro-n-nonanoic acid

In addition, to provide a conservative assessment, it is recommended for purposes of this screening-level evaluation that all additional compounds detected at least once at a concentration at or exceeding 10% (i.e., within one order of magnitude) of their DWEL be considered for inclusion in the HHRA. Table 5-1 shows the percent of the DWEL for all of the detected compounds for which the maximum-detected concentration did not exceed its DWEL. A total of 14 additional compounds not otherwise identified above were detected at a maximum concentration ≥ 10% of their DWELs. These are:

- Acesulfame-K, a sugar substitute, which was detected at a maximum of 11% of its DWEL.
- Atenolol, a beta blocker, which was detected at a maximum of 23% of its DWEL.
- Cotinine, a nicotine degradate, which was detected at a maximum of 16% of its DWEL.,
- Diazepam, an anti-anxiety agent, which was detected at a maximum of 11% of its DWEL.
- Diclofenac, an anti-inflammatory medication, which was detected at a maximum of 31% of its DWEL.
- Dilantin, an anti-seizure medication, which was detected at a maximum of 11% of its DWEL.

- Fluoxetine, an antidepressant, which was detected at a maximum of 22% of its DWEL.
- Gemfibrozil, an antilipidemic, which was detected at a maximum of 14% of its DWEL.
- Lopressor, a beta blocker, which was detected at a maximum of 90% of its DWEL.
- Sucralose, a sugar substitute, which was detected at a maximum of 31% of its DWEL.
- Sulfamethoxazole, a sulfa antibiotic, which was detected at a maximum of 13% of its DWEL.
- TCEP, a flame retardant, which was detected at a maximum of 48% of its DWEL.
- Theophylline, an anti-asthmatic, which was detected at a maximum of 24% of its DWEL.
- Thiabendazole, a fungicide, which was detected at a maximum of 46% of its DWEL.

Note that testosterone (which was detected at a maximum of 15% of its DWEL), PFOA (which was detected at a maximum of 88% of its DWEL), and perfluoro-n-nonanoic acid (which was detected at a maximum of 19% of its DWEL) were also detected at ≥10% of their DWELs but were already identified for inclusion in the HHRA based on being either hormones or PFAS and so are not included in the list immediately above.

All of the compounds recommended for consideration for inclusion in the HHRA are listed in Table 5-3.

Table 5-1. Comparison of Maximum-Detected Concentrations of Residual Chemicals and PFAS in Media of Interest to Health Risk-Based DWELs

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †		DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater		
1,4-Dioxane	Industrial chemical	**850**	**750**	370	
1,7-Dimethylxanthine	Caffeine degradate	36	45	8,300	0.5%
2,4-D	Herbicide	160	20	30,000	0.5%
4-Nonylphenol	Surfactant	3,100	**510,000**	20,000	
4-para-Nonylphenol	Surfactant	240	NA	20,000	1.2%
4-tert-Octylphenol	Surfactant	130	<50	100,000	0.1%
Acesulfame-K	Sugar substitute	13,000	1,000	120,000	10.8%
Acetaminophen	Analgesic	160	39	2,700	5.9%
Albuterol	Anti-asthmatic	**11**	**8.0**	7.5	
Amoxicillin	Antibiotic	33	<20-<80	31,000	0.1%
Atenolol	Beta blocker	230	130	1,000	23.0%
Azithromycin	Antibiotic	<20	NA	25,000	<0.1%
BPA (Bisphenol A)	Plasticizer	<100	28	20,000	0.1%
Bromacil	Herbicide	14	<5	13,000	0.1%
Butalbital	Analgesic	51	54	2,000	2.7%
Caffeine	Stimulant	76	38	20,000,000	<0.1%
Carbadox	Antibiotic	14	<5	33,000	<0.1%
Carbamazepine	Antiseizure	**730**	**850**	330	
Carisoprodol	Muscle relaxant	110	35	10,000	1.1%
Chloramphenicol	Antibiotic	**24**	**<10-<50**	4.1	
Chloridazon	Enzyme	9	62	180,000	<0.1%
Clofibric acid	Cholesterol drug/ Herbicide	120	30	8,300	1.4%
Cotinine	Nicotine degradate	130	25	800	16.3%
Cyanazine	Triazine herbicide	9	<5	1,000	0.9%
DACT	Triazine herbicide	12	<5-<50	3,000	0.4%
DEA	Triazine herbicide	20	<5-<25	3,000	0.7%
DEET	Mosquito repellant	140	500	200,000	0.3%
Dehydronifedipine	Blood pressure drug metabolite	8.7	5.7	1,200	0.7%
Diazepam	Antianxiety	9.3	<5	83	11.2%
Diclofenac	Anti-inflammatory	260	81	830	31.3%
Dilantin	Anti-seizure	130	82	1,200	10.8%
Diltiazem	Calcium blocker	370	5.3	5,000	7.4%
Diuron	Herbicide	100	90	20,000	0.5%
Erythromycin	Antibiotic	25	48	100,000	<0.1%
Estradiol	Estrogenic hormone	**<5-<25**	**35**	0.26	
Estrone	Estrogenic hormone	**1.9**	**<5-<25**	0.058	
Ethinyl estradiol - 17 alpha	Contraceptive hormone	**64**	**49**	0.083	

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †		DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater		
Flumequine	Antibiotic	98	54	25,000	0.4%
Fluoxetine	Antidepressant	210	<10	960	21.9%
Gemfibrozil	Antilipidemic	710	30	5,000	14.2%
Ibuprofen	Analgesic	320	12	8,300	3.9%
Iohexal	X-ray contrast agent	14,000	2,200	500,000	2.8%
Iopromide	X-ray contrast agent	540	37	500,000	0.1%
Ketorolac	Anti-inflammatory	18	5.3	1,600	1.1%
Lidocaine	Antibiotic	550	320	10,000	5.5%
Lincomycin	Antibiotic	76	65	33,000	0.2%
Linuron	Herbicide	6.9	7.9	1,000	0.8%
Lopressor	Beta blocker	900	510	1,000	90.0%
Meclofenamic acid	Anti-inflammatory	300	130	30,000	1.0%
Meprobamate	Anti-anxiety	390	57	22,000	1.8%
Metformin	Antidiabetic	2,600	11	41,000	6.3%
Methylparaben	Preservative	21	48	5,500,000	<0.1%
Naproxen	Analgesic	32	<10-<50	13,000	0.2%
Nifedipine	Calcium blocker	20	<20-<100	1,200	1.7%
N-Nitroso dimethylamine (NDMA)	Industrial solvent	**7.3**	**8.2**	0.86	
Norethisterone	Steroid hormone	**5.9**	**5.0**	1.4	
OUST (Sulfometuron methyl)	Herbicide	11	<5	300,000	<0.1%
Oxolinic acid	Antibiotic	64	<10	110,000	<0.1%
Pentoxifylline	Blood thinner	10	<5	3,300	0.3%
Primidone	Anti-convulsant	**930**	330	410	
Quinoline	Industrial chemical	**28**	<5	3.3	
Salicylic acid	Keratolytic agent	130	<100-<500	13,000	1.0%
Simazine	Triazine herbicide	7.7	<5	730	1.1%
Sucralose	Sugar substitute	90,000	470,000	1,500,000	31.3%
Sulfadiazine	Sulfa antibiotic	14	300	41,000	0.7%
Sulfadimethoxine	Sulfa antibiotic	17	39	1,600,000	<0.1%
Sulfamethoxazole	Sulfa antibiotic	520	700	5,300	13.2%
TCEP	Flame retardant	240	240	500	48.0%
TCPP	Flame retardant	1,300	1,200	200,000	0.7%
TDCPP	Flame retardant	**2,000**	1,300	2,000	
Testosterone	Steroid hormone	7.4	31	200	15.5%
Theobromine	Caffeine degradate	66	490	6,600	7.4%
Theophylline	Anti-asthmatic	120	160	660	24.2%
Thiabendazole	Fungicide	600	9.1	1,300	46.2%
Triclosan	Antimicrobial	130	130	2,300	5.7%
Trimethoprim	Antibiotic	97	17	2,600	3.7%
Perfluoro butanoic acid (PFBA)	PFAS	<10	17	7,000	0.2%

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †		DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater		
Perfluoro octanesulfonate (PFOS)	PFAS	<5	<5	15	<33%
Perfluoro octanesulfonic acid	PFAS	<5	<5	30	<16.6%
Perfluoro octanoic acid (PFOA)	PFAS	22	31	35	88.5%
Perfluoro-1-butanesulfonate	PFAS	13	27	2,000	1.4%
Perfluoro-1-butanesulfonic acid	PFAS	13	26	200,000	<0.1%
Perfluoro-n-heptanoic acid	PFAS	<5	<5	70	<7.2%
Perfluoro-n-hexanoic acid	PFAS	**81**	**80**	70	
Perfluoro-n-nonanoic acid	PFAS	<5	5.7	30	19.0%
Perfluoropentanoic acid	PFAS	**150**	**120**	70	

*Maximum-detected concentrations in reclaimed water or porewater at or exceeding the DWEL are indicated in bold and shaded (dark gray).

†For chemicals that are not detected in a given medium, the laboratory detection limit is noted; where detection limits exceed the DWEL, the value is bolded. For reclaimed water or porewater, these cells are also shaded (light gray).

‡For chemicals with maximum-detected concentrations in reclaimed water or porewater at or exceeding 10% of the DWEL, values are underlined.

DACT – Diaminochlorotriazine; DEA – Desethylatrazine; DEET – N,N-Diethyl-meta-toluamide; TCEP – Tris(2-carboxyethyl)phosphine; TCPP – Tris(1-chloro-2-propyl) phosphate; TDCPP – Tris(1,3-dichloroisopropyl)phosphate

Table 5-2. Summary of Chemicals of Interest with Maximum-Detected Concentrations ≥ DWEL* or 10% of DWEL†

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †		DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater		
1,4-Dioxane	Industrial chemical	**850**	**750**	370	
4-Nonylphenol	Surfactant	3,100	**510,000**	20,000	
Acesulfame-K	Sugar substitute	13,000	1,000	120,000	10.8%
Albuterol	Anti-asthmatic	**11**	**8.0**	7.5	
Atenolol	Beta blocker	230	130	1,000	23.0%
Carbamazepine	Antiseizure	**730**	**850**	330	
Chloramphenicol	Antibiotic	**24**	**<10-<50**	4.1	
Cotinine	Nicotine degradate	130	25	800	16.3%
Diazepam	Antianxiety	9.3	<5	83	11.2%
Diclofenac	Anti-inflammatory	260	81	830	31.3%
Dilantin	Anti-seizure	130	82	1,200	10.8%
Estradiol	Estrogenic hormone	**<5-<25**	**35**	0.26	
Estrone	Estrogenic hormone	**1.9**	**<5-<25**	0.058	
Ethinyl estradiol - 17 alpha	Contraceptive hormone	**64**	**49**	0.083	
Fluoxetine	Antidepressant	210	<10	960	21.9%
Gemfibrozil	Antilipidemic	710	30	5,000	14.2%
Lopressor	Beta blocker	900	510	1,000	90.0%
N-Nitroso dimethylamine (NDMA)	Industrial solvent	**7.3**	**8.2**	0.86	
Norethisterone	Steroid hormone	**5.9**	**5.0**	1.4	
Primidone	Anti-convulsant	**930**	330	410	
Quinoline	Industrial chemical	**28**	<5	3.3	
Sucralose	Sugar substitute	90,000	470,000	1,500,000	31.3%
Sulfamethoxazole	Sulfa antibiotic	520	700	5,300	13.2%
TCEP	Flame retardant	240	240	500	48.0%
TDCPP	Flame retardant	**2,000**	1,300	2,000	
Testosterone	Steroid hormone	7.4	31	200	15.5%
Theophylline	Anti-asthmatic	120	160	660	24.2%
Thiabendazole	Fungicide	600	9.1	1,300	46.2%
Perfluoro octanoic acid (PFOA)	PFAS	22	31	35	88.5%
Perfluoro-n-hexanoic acid	PFAS	**81**	**80**	70	
Perfluoro-n-nonanoic acid	PFAS	<5	5.7	30	19.0%
Perfluoropentanoic acid	PFAS	**150**	**120**	70	

*Maximum-detected concentrations in reclaimed water or porewater at or exceeding the DWEL are indicated in bold and shaded (dark gray).
†For chemicals that are not detected in a given medium, the laboratory detection limit is noted; where detection limits exceed the DWEL, the value is bolded. For reclaimed water or porewater, these cells are also shaded (light gray).
‡For chemicals with maximum-detected concentrations in reclaimed water or porewater at or exceeding 10% of the DWEL, values are underlined.
TCEP – Tris(2-carboxyethyl)phosphine; TDCPP – Tris(1,3-dichloroisopropyl)phosphate

Table 5-3. Chemicals Recommended for Inclusion in the HHRA

Chemical	CAS Number	Category or Pharmaceutical Class	Reason for Inclusion
Hormones			
Androstenedione	63-05-8	Steroid hormone	Hormone
Estradiol	50-28-2	Estrogenic hormone	Exceeds DWEL
Estradiol – 17 beta	50-28-2	Estrogenic hormone	Hormone
Estriol	50-27-1	Hormone	Hormone
Estrone	53-16-7	Estrogenic hormone	Exceeds DWEL
Ethinyl Estradiol - 17 alpha	57-63-6	Contraceptive hormone	Exceeds DWEL
Norethisterone	68-22-4	Steroid hormone	Exceeds DWEL
Progesterone	57-83-0	Steroid hormone	Hormone
Testosterone	58-22-0	Steroid hormone	Hormone and ≥ 10% DWEL but < DWEL
PPCPs and Other Personal Products			
Acesulfame-K	55589-62-3	Sugar substitute	≥ 10% DWEL but < DWEL
Albuterol	18559-94-9	Anti-asthmatic	Exceeds DWEL
Atenolol	29122-68-7	Beta blocker	≥ 10% DWEL but < DWEL
Carbamazepine	298-46-4	Antiseizure	Exceeds DWEL
Chloramphenicol	56-75-7	Antibiotic	Exceeds DWEL
Cotinine	486-56-6	Nicotine degradate	≥ 10% DWEL but < DWEL
Diazepam	439-14-5	Antianxiety	≥ 10% DWEL but < DWEL
Diclofenac	15307-86-5	Anti-inflammatory	≥ 10% DWEL but < DWEL
Dilantin	57-41-0	Antisiezure	≥ 10% DWEL but < DWEL
Fluoxetine	54910-89-3	Antidepressant	≥ 10% DWEL but < DWEL
Gemfibrozil	25812-30-0	Antilipidemic	≥ 10% DWEL but < DWEL
Lopressor	51384-51-1	Beta Blocker	≥ 10% DWEL but < DWEL
Primidone	125-33-7	Anti-convulsant	Exceeds DWEL
Sucralose	56038-13-2	Sugar substitute	≥ 10% DWEL but < DWEL
Sulfamethoxazole	723-46-6	Sulfa antibiotic	≥ 10% DWEL but < DWEL
Theophylline	58-55-9	Anti-asthmatic	≥ 10% DWEL but < DWEL
Industrial chemicals and Pesticides			
1,4-Dioxane	123-91-1	Industrial chemical	Exceeds DWEL
4-Nonylphenol	104-40-5	Surfactant	Exceeds DWEL

Table 5-3. Chemicals Recommended for Inclusion in the HHRA

	Chemical	CAS Number	Category or Pharmaceutical Class	Reason for Inclusion
	N-Nitroso dimethylamine (NDMA)	62-75-9	Industrial solvent	Exceeds DWEL
	Quinoline	91-22-5	Industrial chemical	Exceeds DWEL
	Thiabendazole	148-79-8	Fungicide	≥ 10% DWEL but < DWEL
	Tris(2-carboxyethyl)phosphine (TCEP)	115-96-8	Flame retardant	≥ 10% DWEL but < DWEL
	Tris(1,3-dichloroisopropyl)phosphate (TDCPP)	13674-87-8	Flame retardant	Exceeds DWEL
Perfluorochemicals				
	Perfluoro butanoic acid (PFBA)	375-22-4	Perfluorochemical	PFAS
	Perfluoro octanesulfonate (PFOS)	45298-90-6	Perfluorochemical	PFAS
	Perfluoro octanesulfonic acid	1763-23-1	Perfluorochemical	PFAS
	Perfluoro octanoic acid (PFOA)	15899-31-7	Perfluorochemical	PFAS and ≥ 10% DWEL but < DWEL
	Perfluoro-1-butanesulfonate	194999-85-4	Perfluorochemical	PFAS
	Perfluoro-1-butanesulfonic acid	375-73-5	Perfluorochemical	PFAS
	Perfluoro-1-hexanesulfonate	108427-53-8	Perfluorochemical	PFAS
	Perfluoro-1-hexanesulfonic acid	355-46-4	Perfluorochemical	PFAS
	Perfluoro-n-decanoic acid	335-76-2	Perfluorochemical	PFAS
	Perfluoro-n-heptanoic acid	375-85-9	Perfluorochemical	PFAS
	Perfluoro-n-hexanoic acid	307-24-4	Perfluorochemical	Exceeds DWEL
	Perfluoro-n-nonanoic acid	375-95-1	Perfluorochemical	≥ 10% DWEL but < DWEL
	Perfluoropentanoic acid	2706-90-3	Perfluorochemical	Exceeds DWEL

DWEL – Drinking Water Equivalent Level (established in Screening-Level Evaluation); PFAS – polyfluoroalkyl substances; PPCP – pharmaceutical and personal care product ingredients

6.0 CONCLUSIONS AND RECOMMENDATIONS

The results of this screening-level evaluation show that 15 compounds were detected at least once in reclaimed water and or porewater at a concentration in excess of their DWELs. Since these compounds include four hormones and two PFAS, inclusion of all hormones and PFAS analyzed in the RWIS (five additional hormones and 11 additional PFAS) in the HHRA is recommended. In addition, to provide a conservative assessment, inclusion of 14 additional compounds that were detected at a maximum concentration ≥ 10% of their DWEL is also recommended.

Overall, based on the results of this screening-level evaluation, nine hormones, 16 PPCPs and other personal product ingredients, seven industrial chemicals or pesticides, and 13 PFAS (45 compounds total), are recommended for consideration for inclusion in the HHRA.

This screening-level evaluation is conducted using conservative assumptions about the concentrations to which persons could be exposed (i.e., the assessment assumes that, every day, a person could drink their daily per capita amount of drinking water containing the maximum concentration of each COI that was detected in reclaimed water or porewater). Repeated daily exposure to concentrations of this magnitude and at this rate from reclaimed water is unlikely. However, because of the conservative methods applied, if detected concentrations of a compound do not exceed the DWEL (or are at <10% of their DWEL), significant human health risks from exposure to these compounds in reclaimed water are extremely unlikely. The HHRA will more closely investigate potential exposure scenarios and derive realistic estimates of human exposure, as well as more closely investigate the toxicological hazard of COIs.

7.0 REFERENCES

ATSDR. 2007. *Minimal Risk Levels (MRLs) for Hazardous Substances.* Agency for Toxic Substances and Disease Registry. Centers for Disease Control, Atlanta, GA.

Blackburn K, Stickney JA, Carlson-Lynch HL, McGinnis PM, Chappell L, and Felter SP. 2005. Application of the threshold of toxicological concern approach to ingredients in personal and household care products. *Regul Toxicol Pharmacol*. 43(3):249-259.

Cheeseman MA, Machuga EJ, and Bailey AB. 1999. A tiered approach to threshold of regulation. *Food Chem Toxicol*. 37(4):387-412.

Cramer GM, Ford RA, and Hall RL. 1978. Estimation of toxic hazard—a decision tree approach. *Food Cosmetics Toxicol*. 16:255-276.

Dolan DG, Naumann BD, Sargent EV, Maier A, and Dourson M. 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. *Regul Toxicol Pharmacol*. 43(1):1-9.

EMEA. 1998. *Committee for Veterinary Medicinal Products: Enrofloxacin, Summary Report*. European Agency for the Evaluation of Medicinal Products. London, UK.

FDA. 2005. *Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers*. Food and Drug Administration. Washington, D.C.

Gaylor DW and Gold LS. 1995. Quick estimate of the regulatory virtually safe dose based on the maximum tolerated dose for rodent bioassays. *Regul Toxicol Pharmacol*. 22(1):57-63.

Gold LS, Bruce BN, Bernstein L, Blumenthal M, Chow K, and Da Costa M. 2011. The Carcinogenic Potency Database (CPDB). Lawrence Berkeley Laboratory, Berkeley, CA, from https://www.toxinfo.io/

HDR. 2017a. Groundwater quality characterization (Task 1.1). LOTT Clean Water Alliance reclaimed water infiltration study. Technical memorandum. HDR, Olympia, WA.

HDR. 2017b. Surface water quality characterization (Task 1.2). LOTT Clean Water Alliance reclaimed water infiltration study. Technical memorandum. HDR, Olympia, WA.

HDR. 2017c. Wastewater and reclaimed water quality characterization (Task 1.3). LOTT Clean Water Alliance reclaimed water infiltration study. Technical memorandum. HDR, Olympia, WA.

Intertox. 2015. Development of a Water Utility Primer on EDCs/PPCPs: Technical Summary. Prepared by Intertox, Inc., for the Water Research Foundation. Gretchen Bruce, Principal Investigator.

KnowledgeBase. 2020 Antimicrobial Index. Bellingham, WA. Accessed May 28, 2020 at http://antibiotics.toku-e.com/

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, and Würtzen G. 2004. European branch of the international life sciences institute. structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem Toxicol*. 42(1):65-83.

Munro I, Ford R, Kennepohl E, and Sprenger JG. 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. *Food Chem Toxicol*. 34(9):829-867.

Schwab BWH, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, and Anderson PD. 2005. Human pharmaceuticals in US surface waters: a human health risk assessment. *Regul Toxicol Pharmacol*. 42(3):296-312.

Snyder SA, Stanford BD, Bruce GM, Pleus RC, and Drewes JE. 2010. *Identifying Hormonally Active Compounds, Pharmaceuticals, and Personal Care Product Ingredients of Health Concern from Potential Presence in Water Intended for Indirect Potable Reuse*. Water Reuse Foundation Project No. 05-005. Alexandria, VA.

U.S. EPA. 1993. *Reference Dose (RfD): Description and Use in Health Risk Assessments*. United States Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments.

U.S. EPA. 2002. *A Review of the Reference Dose and Reference Concentration Processes*. EPA/630/P-02/002F. U.S. Environmental Protection Agency. Washington, D.C.

U.S. EPA. 2004. *Estimated Per Capita Water Ingestion and Body Weight in the United States–An Update*. United States Environmental Protection Agency. Washington D.C. EPA-822-R-00-001. October.

U.S. EPA. 2005. *Guidelines for Carcinogen Risk Assessment*. Office of the Science Advisor, U.S. Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at http://www.epa.gov/cancerguidelines/.

U.S. EPA. 2008. *Risk Assessment Portal. Step 2: Dose-Response Assessment*. United States Environmental Protection Agency. Washington, D.C.

U.S. EPA. 2012a. *Benchmark Dose Software (BMDS).* U.S. Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at https://www.epa.gov/bmds

U.S. EPA. 2012b. Water: Contaminant Candidate List 3—CCL. Office of Water, U.S. Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at http://water.epa.gov/scitech/drinkingwater/dws/ccl/ccl3.cfm.

U.S. EPA, 2018. *2018 Edition of the Drinking Water Standards and Health Advisories Tables*. U.S. Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

U.S. EPA. 2019. *Update for Chapter 3 of the Exposure Factors Handbook: Ingestion of Water and Other Select Liquids*. United States Environmental Protection Agency. Washington D.C. EPA/600/R-18-259F. February. Accessed May 28, 2020 at https://www.epa.gov/sites/production/files/2019-02/documents/efh_-_chapter_3_update.pdf.

WHO. 1994. *Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-Based Exposure Limits. Environmental Health Criteria 170*. World Health Organization. Geneva.

WHO. 1997. *Enrofloxacin WHO Food Additive Series 39*. World Health Organization. Geneva Accessed May 28, 2020 at http://www.inchem.org/documents/jecfa/jecmono/v34je05.htm.

WHO. 2006. Propyl paraben, addendum. Prepared by S. Barlow, A. Mattia, and J-C. Leblanc. In: Safety evaluation of certain food additives and contaminants. *WHO Food Additives 58*. World Health Organization. Geneva. Accessed May 28, 2020 at https://apps.who.int/iris/bitstream/handle/10665/43645/9789241660587_eng.pdf?sequence=1.

APPENDIX A

SUMMARY OF MAXIMUM DETECTED CONCENTRATIONS IN EACH MEDIUM AND COMPARISON TO DWELS

Table A-1. Maximum-Detected Concentrations of Residual Chemicals Detected in Reclaimed Water and Porewater Compared to Concentrations in Effluent Water, Groundwater, and Surface Water

		Maximum-Detected Concentration (ng/L)				
Chemical	Category or Pharmaceutical Class	Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water
1,4-Dioxane	Industrial chemical	850	750	NA	690	NA
1,7-Dimethylxanthine	Caffeine degradate	36	45	<10	17	<10
2,4-D	Herbicide	160	20	31	<5-<25	36
4-Nonylphenol	Surfactant	3,100	510,000	1,700	3,100	220
4-para-Nonylphenol	Surfactant	240	NA	NA	NA	NA
4-tert-Octylphenol	Surfactant	130	<50	84	150	170
Acesulfame-K	Sugar substitute	13,000	1,000	13,000	23,000	630
Acetaminophen	Analgesic	160	39	<5	16	<5
Albuterol	Anti-asthmatic	11	8.0	80	31	<5
Amoxicillin	Antibiotic	33	<20-<80	22,000	140	<20
Atenolol	Beta blocker	230	130	270	14	14
Bisphenol A	Plasticizer	<100	28	<10	53	<10
Bromacil	Herbicide	14	<5	<5	5.9	<5
Butalbital	Analgesic	51	54	6.8	48	<5
Caffeine	Stimulant	76	38	12	340	<5
Carbadox	Antibiotic	14	<5	<5	5.2	<5
Carbamazepine	Antiseizure	730	850	410	760	10
Carisoprodol	Muscle relaxant	110	35	18	25	<5
Chloramphenicol	Antibiotic	24	<10-<50	<10	<10-<50	<10
Chloridazon	Enzyme	9	62	<5	7.5	<5
Clofibric Acid	Cholesterol drug/ Herbicide	120	30	<5	6.0	<5
Cotinine	Nicotine degradate	130	25	21	0<1	44
Cyanazine	Triazine herbicide	9	<5	<5	15	9.2
DACT	Triazine herbicide	12	<5-<50	<5	8.2	23
DEA	Triazine herbicide	20	<5-<25	<5	<5-<25	<5
DEET	Mosquito repellant	140	500	41	30	390
Dehydronifedipine	Blood pressure drug metabolite	8.7	5.7	<5	22	<5
Diazepam	Antianxiety	9.3	<5	5	<5	<5
Diclofenac	Anti-inflammatory	260	81	50	6.9	7.4
Dilantin	Anti-seizure	130	82	59	<20	<20
Diltiazem	Calcium blocker	370	5.3	42	<5	<5
Diuron	Herbicide	100	90	<5	56	<5
Erythromycin	Antibiotic	25	48	24	22	<10
Estradiol	Estrogenic hormone	<5-<25	35	NA	14	<5
Estrone	Estrogenic hormone	1.9	<5-<25	<0.5	<5-<25	2.0

Chemical	Category or Pharmaceutical Class	Maximum-Detected Concentration (ng/L)				
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water
Ethinyl estradiol - 17 alpha	Contraceptive hormone	64	49	<5	<5	<5
Flumequine	Antibiotic	98	54	<10	<10	<10
Fluoxetine	Antidepressant	210	<10	56	12	<10
Gemfibrozil	Antilipidemic	710	30	620	10	<5
Ibuprofen	Analgesic	320	12	<10	19	<10
Iohexal	X-ray contrast agent	14,000	2,200	12,000	97	33
Iopromide	X-ray contrast agent	540	37	92	7.8	59
Ketorolac	Anti-inflammatory	18	5.3	<5	5.4	<5
Lidocaine	Antibiotic	550	320	370	70	<5
Lincomycin	Antibiotic	76	65	<10	41	14
Linuron	Herbicide	6.9	7.9	<5	7.8	<5
Lopressor	Beta blocker	900	510	690	<20	<20
Meclofenamic acid	Anti-inflammatory	300	130	<5	10	<5
Meprobamate	Anti-anxiety	390	57	40	36	<5
Metformin	Antidiabetic	2,600	11	NA	690	NA
Methylparaben	Preservative	21	48	<20	<20-<100	46
Naproxen	Analgesic	32	<10-<50	<10	<10-<50	<10
Nifedipine	Calcium blocker	20	<20-<100	<20	<20-<100	<20
N-Nitroso dimethylamine (NDMA)	Industrial solvent	7.3	8.2	NA	6.4	NA
Norethisterone	Steroid hormone	5.9	5.0	<5	<5	<5
OUST (Sulfometuron methyl)	Herbicide	11	<5	NA	<5	NA
Oxolinic acid	Antibiotic	64	<10	<10	<10	<10
Pentoxifylline	Blood thinner	10	<5	6.2	<5	<5
Primidone	Anti-convulsant	930	330	230	120	<5
Quinoline	Industrial chemical	28	<5	<5	19	20
Salicylic Acid	Keratolytic agent	130	<100-<500	NA	<100-<500	NA
Simazine	Triazine herbicide	7.7	<5	<5	25	<5
Sucralose	Sugar substitute	90,000	470,000	44,000	82,000	6,300
Sulfadiazine	Sulfa antibiotic	14	300	<5	<5-<20	<5
Sulfadimethoxine	Sulfa antibiotic	17	39	<5	19	<5
Sulfamethoxazole	Sulfa antibiotic	520	700	810	970	15
TCEP	Flame retardant	240	240	280	200	14
TCPP	Flame retardant	1,300	1,200	730	280	<100
TDCPP	Flame retardant	2,000	1,300	340	960	4,500
Testosterone	Steroid hormone	7.4	31	<5	<5	<5
Theobromine	Caffeine degradate	66	490	110	18	<10
Theophylline	Anti-asthmatic	120	160	NA	68	NA
Thiabendazole	Fungicide	600	9.1	<5	5.5	<5

Chemical	Category or Pharmaceutical Class	Maximum-Detected Concentration (ng/L)				
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water
Triclosan	Antimicrobial	130	130	73	57	16
Trimethoprim	Antibiotic	97	17	450	<5	<5

NA – Not analyzed; DACT – Diaminochlorotriazine; DEA – Desethylatrazine; DEET – N,N-Diethyl-meta-toluamide; TCEP – Tris(2-carboxyethyl)phosphine; TCPP – Tris(1-chloro-2-propyl) phosphate; TDCPP – Tris(1,3-dichloroisopropyl)phosphate

Table A-2. Maximum-Detected Concentrations of PFAS Detected in Reclaimed Water and Porewater Compared to Concentrations in Effluent Water, Groundwater, and Surface Water

	Maximum-Detected Concentration (ng/L)				
Chemical	**Reclaimed Water**	**Porewater**	**Effluent Water**	**Ground-water**	**Surface Water**
Perfluoro butanoic acid (PFBA)	<10	17	NA	12	NA
Perfluoro octanesulfonate (PFOS)	<5	<5	NA	5.7	NA
Perfluoro octanesulfonic acid	<5	<5	NA	5.7	NA
Perfluoro octanoic acid (PFOA)	22	31	NA	29	NA
Perfluoro-1-butanesulfonate	13	27	NA	23	NA
Perfluoro-1-butanesulfonic acid	13	26	NA	22	NA
Perfluoro-n-heptanoic acid	<5	<5	NA	5.0	NA
Perfluoro-n-hexanoic acid	81	80	NA	62	NA
Perfluoro-n-nonanoic acid	<5	5.7	NA	8.6	NA
Perfluoropentanoic acid	150	120	NA	94	NA

NA – Not analyzed

Table A-3. Detection Limits of Compounds Analyzed for But Never Detected in Reclaimed Water or Porewater

	Range of Detection limits (number of samples)	
Chemical	**Reclaimed water (ng/L)**	**Porewater (ng/L)**
4-n-Octylphenol diethoxylate	100 (15)	NA
4-n-Octylphenol monoethoxylate	100 (15)	NA
Androstenedione	5 - 10 (27)	5 - 10 (23)
Atrazine	5 (27)	5 (23)
Azithromycin	20 (7)	NA
Bendroflumethiazide	5 - 25 (27)	5 - 25 (23)
Bezafibrate	5 (27)	5 (23)
Butylparben	5 - 25 (27)	5 - 25 (23)
Chlorotoluron	5 (27)	5 (23)
Cimetidine	5 (27)	5 (23)
DIA	5 - 25 (27)	5 - 25 (23)
Estradiol - 17 beta	0.5 - 5 (30)	NA
Estriol	10 - 50 (12)	10 - 50 (23)
Ethylparaben	20 - 100 (27)	20 - 100 (23)
Isobutylparaben	5 - 25 (27)	5 - 25 (23)
Isoproturon	100 (27)	100 (23)
Ketoprofen	5 (27)	5 (23)
Metazachlor	5 (24)	5 (18)
Metolachlor	5 (9)	5 (17)
Nonylphenol Diethoxylate	100 (15)	NA
Nonylphenol Monoethoxylate	100 (15)	NA
Octylphenol	100 (5)	NA
Phenazone	5 (27)	5 (23)
Progesterone	5 (27)	5 (23)
Propazine	5 (27)	5 (23)
Propylparaben	5 - 25 (27)	5 - 25 (23)
Sulfachloropyridazine	5 (27)	5 (23)
Sulfamerazine	5 - 25 (27)	5 - 25 (23)
Sulfamethazine	5 (27)	5 (23)
Sulfamethizole	5 (27)	5 (23)
Sulfathiazole	5 - 20 (27)	5 - 20 (23)
Triclocarban	5 - 10 (27)	5 - 10 (23)
Warfarin	5 (27)	5 (23)
Perfluoro octanesulfonate-PFOS	5 (27)	5 (24)
Perfluoro octanesulfonic acid - PFOS	5 (27)	5 (24)
Perfluoro-1-hexanesulfonate	5 (27)	5 (24)
Perfluoro-1-hexanesulfonic acid	5 (27)	5 (24)
Perfluoro-n-decanoic acid	5 (27)	5 (24)
Perfluoro-n-heptanoic acid	5 (27)	5 (24)

NA – Not analyzed

Table A-3. Comparison of Maximum-Detected Concentrations of Residual Chemicals and PFAS in All Media to Health Risk-Based DWELs

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡	Max % of DWEL (for Groundwater)
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water			
1,4-Dioxane	Industrial chemical	**850**	**750**	NA	690	NA	370		186.5%
1,7-Dimethylxanthine	Caffeine degradate	36	45	<10	17	<10	8,300	0.5%	0.2%
2,4-D	Herbicide	160	20	31	<5-<25	36	30,000	0.5%	NA
4-Nonylphenol	Surfactant	3,100	**510,000**	1,700	3,100	220	20,000		15.5%
4-para-Nonylphenol	Surfactant	240	NA	NA	NA	NA	20,000	1.2%	NA
4-tert-Octylphenol	Surfactant	130	<50	84	150	170	100,000	0.1%	0.2%
Acesulfame-K	Sugar substitute	13,000	1,000	13,000	23,000	630	120,000	10.8%	19.2%
Acetaminophen	Analgesic	160	39	<5	16	<5	2,700	5.9%	0.6%
Albuterol	Anti-asthmatic	11	8.0	**80**	**31**	<5	7.5		413.3%
Amoxicillin	Antibiotic	33	<20-<80	22,000	140	<20	31,000	0.1%	0.5%
Atenolol	Beta blocker	230	130	270	14	14	1,000	23.0%	1.4%
Azithromycin	Antibiotic	<20	NA	65	200	94	25,000	<0.1%	0.8%
BPA (Bisphenol A)	Plasticizer	<100	28	<10	53	<10	20,000	0.1%	0.3%
Bromacil	Herbicide	14	<5	<5	5.9	<5	13,000	0.1%	<0.1%
Butalbital	Analgesic	51	54	6.8	48	<5	2,000	2.7%	2.4%
Caffeine	Stimulant	76	38	12	340	<5	20,000,000	<0.1%	<0.1%
Carbadox	Antibiotic	14	<5	<5	5.2	<5	33,000	<0.1%	<0.1%
Carbamazepine	Antiseizure	**730**	**850**	410	760	10	330		230.3%
Carisoprodol	Muscle relaxant	110	35	18	25	<5	10,000	1.1%	0.3%
Chloramphenicol	Antibiotic	**24**	**<10-<50**	<10	**<10-<50**	<10	4.1		NA
Chloridazon	Enzyme	9	62	<5	7.5	<5	180,000	<0.1%	<0.1%
Clofibric acid	Cholesterol drug/ Herbicide	120	30	<5	6.0	<5	8,300	1.4%	0.1%
Cotinine	Nicotine degradate	130	25	21	<10	44	800	16.3%	NA

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡	Max % of DWEL (for Groundwater)
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water			
Cyanazine	Triazine herbicide	9	<5	<5	15	9.2	1,000	0.9%	1.5%
DACT	Triazine herbicide	12	<5-<50	<5	8.2	23	3,000	0.4%	0.3%
DEA	Triazine herbicide	20	<5-<25	<5	<5-<25	<5	3,000	0.7%	NA
DEET	Mosquito repellant	140	500	41	30	390	200,000	0.3%	0.0%
Dehydronifedipine	Blood pressure drug metabolite	8.7	5.7	<5	22	<5	1,200	0.7%	1.8%
Diazepam	Antianxiety	9.3	<5	5	<5	<5	83	11.2%	NA
Diclofenac	Anti-inflammatory	260	81	50	6.9	7.4	830	31.3%	0.8%
Dilantin	Anti-seizure	130	82	59	<20	<20	1,200	10.8%	NA
Diltiazem	Calcium blocker	370	5.3	42	<5	<5	5,000	7.4%	NA
Diuron	Herbicide	100	90	<5	56	<5	20,000	0.5%	0.3%
Erythromycin	Antibiotic	25	48	24	22	<10	100,000	<0.1%	<0.1%
Estradiol	Estrogenic hormone	**<5-<25**	**35**	NA	**14**	**<5**	0.26		5384.6%
Estrone	Estrogenic hormone	**1.9**	**<5-<25**	<0.5	**<5-<25**	**2.0**	0.058		NA
Ethinyl estradiol - 17 alpha	Contraceptive hormone	**64**	**49**	<5	**<5**	**<5**	0.083		NA
Flumequine	Antibiotic	98	54	<10	<10	<10	25,000	0.4%	NA
Fluoxetine	Antidepressant	210	<10	56	12	<10	960	21.9%	1.3%
Gemfibrozil	Antilipidemic	710	30	620	10	<5	5,000	14.2%	0.2%
Ibuprofen	Analgesic	320	12	<10	19	<10	8,300	3.9%	0.2%
Iohexal	X-ray contrast agent	14,000	2,200	12,000	97	33	500,000	2.8%	<0.1%
Iopromide	X-ray contrast agent	540	37	92	7.8	59	500,000	0.1%	<0.1%
Ketorolac	Anti-inflammatory	18	5.3	<5	5.4	<5	1,600	1.1%	0.3%
Lidocaine	Antibiotic	550	320	370	70	<5	10,000	5.5%	0.7%

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡	Max % of DWEL (for Groundwater)
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water			
Lincomycin	Antibiotic	76	65	<10	41	14	33,000	0.2%	0.1%
Linuron	Herbicide	6.9	7.9	<5	7.8	<5	1,000	0.8%	0.8%
Lopressor	Beta blocker	900	510	690	<20	<20	1,000	90.0%	NA
Meclofenamic acid	Anti-inflammatory	300	130	<5	10	<5	30,000	1.0%	<0.1%
Meprobamate	Anti-anxiety	390	57	40	36	<5	22,000	1.8%	0.2%
Metformin	Antidiabetic	2,600	11	NA	690	NA	41,000	6.3%	1.7%
Methylparaben	Preservative	21	48	<20	<20-<100	46	5,500,000	<0.1%	NA
Naproxen	Analgesic	32	<10-<50	<10	<10-<50	<10	13,000	0.2%	NA
Nifedipine	Calcium blocker	20	<20-<100	<20	<20-<100	<20	1,200	1.7%	NA
N-Nitroso dimethylamine (NDMA)	Industrial solvent	**7.3**	**8.2**	NA	**6.4**	NA	0.86		744.2%
Norethisterone	Steroid hormone	**5.9**	**5.0**	<5	**<5**	**<5**	1.4		NA
OUST (Sulfometuron methyl)	Herbicide	11	<5	NA	<5	NA	300,000	<0.1%	NA
Oxolinic acid	Antibiotic	64	<10	<10	<10	<10	110,000	<0.1%	NA
Pentoxifylline	Blood thinner	10	<5	6.2	<5	<5	3,300	0.3%	NA
Primidone	Anti-convulsant	930	**330**	230	120	<5	410		29.3%
Quinoline	Industrial chemical	**28**	<5	<5	**19**	**20**	3.3		575.8%
Salicylic acid	Keratolytic agent	130	<100-<500	NA	<100-<500	NA	13,000	1.0%	NA
Simazine	Triazine herbicide	7.7	<5	<5	25	<5	730	1.1%	3.4%
Sucralose	Sugar substitute	90,000	470,000	44,000	82,000	6,300	1,500,000	31.3%	5.5%
Sulfadiazine	Sulfa antibiotic	14	300	<5	<5-<20	<5	41,000	0.7%	NA
Sulfadimethoxine	Sulfa antibiotic	17	39	<5	19	<5	1,600,000	<0.1%	<0.1%
Sulfamethoxazole	Sulfa antibiotic	520	700	810	970	15	5,300	13.2%	18.3%
TCEP	Flame retardant	240	240	280	200	14	500	48.0%	40.0%
TCPP	Flame retardant	1,300	1,200	730	280	<100	200,000	0.7%	0.1%
TDCPP	Flame retardant	**2,000**	1,300	340	960	**4,500**	2,000		48.0%

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡	Max % of DWEL (for Groundwater)
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water			
Testosterone	Steroid hormone	7.4	31	<5	<5	<5	200	15.5%	NA
Theobromine	Caffeine degradate	66	490	110	18	<10	6,600	7.4%	0.3%
Theophylline	Anti-asthmatic	120	160	NA	68	NA	660	24.2%	10.3%
Thiabendazole	Fungicide	600	9.1	<5	5.5	<5	1,300	46.2%	0.4%
Triclosan	Antimicrobial	130	130	73	57	16	2,300	5.7%	NA
Trimethoprim	Antibiotic	97	17	450	<5	<5	2,600	3.7%	2.5%
Perfluoro butanoic acid (PFBA)	PFAS	<10	17	NA	12	NA	7,000	0.2%	0.2%
Perfluoro octanesulfonate (PFOS)	PFAS	<5	<5	NA	5.7	NA	15	<33%	38.0%
Perfluoro octanesulfonic acid	PFAS	<5	<5	NA	5.7	NA	30	<16.6%	19.0%
Perfluoro octanoic acid (PFOA)	PFAS	22	31	NA	29	NA	35	88.5%	82.9%
Perfluoro-1-butanesulfonate	PFAS	13	27	NA	23	NA	2,000	1.4%	1.2%
Perfluoro-1-butanesulfonic acid	PFAS	13	26	NA	22	NA	200,000	<0.1%	<0.1%
Perfluoro-n-heptanoic acid	PFAS	<5	<5	NA	5.0	NA	70	<7.2%	7.1%
Perfluoro-n-hexanoic acid	PFAS	**81**	**80**	NA	62	NA	70		88.6%
Perfluoro-n-nonanoic acid	PFAS	<5	5.7	NA	8.6	NA	30	19.0%	28.7%
Perfluoropentanoic acid	PFAS	**150**	**120**	NA	**94**	NA	70		134.3%

*Maximum-detected concentrations in reclaimed water or porewater at or exceeding the DWEL are indicated in bold and shaded (dark gray).
†For chemicals that are not detected in a given medium, the laboratory detection limit is noted; where detection limits exceed the DWEL, the value is bolded. For reclaimed water or porewater, these cells are also shaded (light gray).
‡For chemicals with maximum-detected concentrations in reclaimed water or porewater at or exceeding 10% of the DWEL, values are underlined.
DACT – Diaminochlorotriazine; DEA – Desethylatrazine; DEET – N,N-Diethyl-meta-toluamide; NA – Not analyzed; TCEP – Tris(2-carboxyethyl)phosphine; TCPP – Tris(1-chloro-2-propyl) phosphate; TDCPP – Tris(1,3-dichloroisopropyl)phosphate

Table A-4. Summary of Chemicals of Interest with Maximum-Detected Concentrations ≥ DWEL* or 10% of DWEL†

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water		
1,4-Dioxane	Industrial chemical	**850**	**750**	NA	690	NA	370	
4-Nonylphenol	Surfactant	3,100	**510,000**	1,700	3,100	220	20,000	
Acesulfame-K	Sugar substitute	13,000	1,000	13,000	23,000	630	120,000	10.8%
Albuterol	Anti-asthmatic	11	8.0	**80**	**31**	<5	7.5	
Atenolol	Beta blocker	230	130	270	14	14	1,000	23.0%
Carbamazepine	Antiseizure	**730**	**850**	410	760	10	330	
Chloramphenicol	Antibiotic	**24**	**<10-<50**	<10	**<10-<50**	<10	4.1	
Cotinine	Nicotine degradate	130	25	21	<10	44	800	16.3%
Diazepam	Antianxiety	9.3	<5	5	<5	<5	83	11.2%
Diclofenac	Anti-inflammatory	260	81	50	6.9	7.4	830	31.3%
Dilantin	Anti-seizure	130	82	59	<20	<20	1,200	10.8%
Estradiol	IEstrogenic hormone	**<5-<25**	**35**	NA	**14**	**<5**	0.26	
Estrone	Estrogenic hormone	**1.9**	**<5-<25**	<0.5	**<5-<25**	**2.0**	0.058	
Ethinyl estradiol - 17 alpha	Contraceptive hormone	**64**	**49**	<5	**<5**	**<5**	0.083	
Fluoxetine	Antidepressant	210	<10	56	12	<10	960	21.9%
Gemfibrozil	Antilipidemic	710	30	620	10	<5	5,000	14.2%
Lopressor	Beta blocker	900	510	690	<20	<20	1,000	90.0%
N-Nitroso dimethylamine (NDMA)	Industrial solvent	**7.3**	**8.2**	NA	**6.4**	NA	0.86	
Norethisterone	Steroid hormone	**5.9**	**5.0**	<5	**<5**	**<5**	1.4	
Primidone	Anti-convulsant	930	**330**	230	120	<5	410	
Quinoline	Industrial chemical	**28**	<5	<5	**19**	**20**	3.3	
Sucralose	Sugar substitute	90,000	470,000	44,000	82,000	6,300	1,500,000	31.3%
Sulfamethoxazole	Sulfa antibiotic	520	700	810	970	15	5,300	13.2%
TCEP	Flame retardant	240	240	280	200	14	500	48.0%
TDCPP	Flame retardant	**2,000**	1,300	340	960	**4,500**	2,000	
Testosterone	Steroid hormone	7.4	31	<5	<5	<5	200	15.5%

Chemical	Category or Pharmaceutical Class	Maximum Detected Concentration (ng/L)*, †					DWEL (ng/L)	Max % of DWEL (for Reclaimed or Porewater, if <DWEL)‡
		Reclaimed Water	Porewater	Effluent Water	Ground-water	Surface Water		
Theophylline	Anti-asthmatic	120	160	NA	68	NA	660	24.2%
Thiabendazole	Fungicide	600	9.1	<5	5.5	<5	1,300	46.2%
Perfluoro octanoic acid (PFOA)	PFAS	22	31	NA	29	NA	35	88.5%
Perfluoro-n-hexanoic acid	PFAS	**81**	**80**	NA	62	NA	70	
Perfluoro-n-nonanoic acid	PFAS	<5	5.7	NA	8.6	NA	30	19.0%
Perfluoropentanoic acid	PFAS	**150**	**120**	NA	**94**	NA	70	

*Maximum-detected concentrations in reclaimed water or porewater at or exceeding the DWEL are indicated in bold and shaded (dark gray).
†For chemicals that are not detected in a given medium, the laboratory detection limit is noted; where detection limits exceed the DWEL, the value is bolded. For reclaimed water or porewater, these cells are also shaded (light gray).
‡For chemicals with maximum-detected concentrations in reclaimed water or porewater at or exceeding 10% of the DWEL, values are underlined.
NA – Not analyzed; TCEP – Tris(2-carboxyethyl)phosphine; TDCPP – Tris(1,3-dichloroisopropyl)phosphate

APPENDIX B

SUMMARY OF ESTIMATED COMPARISON LEVELS AND CORRESPONDING DWELS

Table B-1. Published Acceptable Daily Intakes (ADIs) for Residual Chemicals Detected in Water

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
1,4-Dioxane	0.44 (WA MTCA GWC Method B; WA DEQ, 2020); 4.4 (WA MTCA GWC Method C; WA DEQ, 2020)	0.03 (U.S. EPA, 2013)	0.1 (ATSDR, 2012a)	30 (OEHHA, 2020a)	---	0.35 µg/L (USEPA corresponding to 10^{-6}, see CalEPA, 2019); 1 µg/L (NL; CalEPA, 2019); 35 µg/L (NL; CalEPA, 2019); 1 µg/L (HBV; MDH, 2020); 7 µg/L (HA; U.S. EPA, 1987b)	0.1 (U.S. EPA, 2013); 0.027 (OEHHA, 2020a)	0.37	**Cancer SF (OEHHA, 2020a)**
1,7-Dimethylxanthine	*No values*	---	---	---	---	---	---	---	---
2,4-D	70 (MCL; U.S. EPA, 2020); 100 (WA WQS; WAC 173-200, 1990); 160 (WA MTCA GWC Method B; WA DEQ, 2020); 350 (WA MTCA GWC Method C; WA DEQ, 2020)	0.01	0.009 (ATSDR, 2017a)	---	---	0.01 mg/kg-d (WHO, 1996); 30 µg/L (chronic HRL; MDH, 2020)	---	30	**Chronic HRL (MDH, 2020)**
4-Nonylphenol	---	---	---	---	---	20 µg/L (HBV; MDH, 2020)	---	20	**HBV (MDH, 2020)**

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
4-para-Nonylphenol	---	---	---	---	---	20 µg/L (HBV; MDH, 2020)	---	20	**HBV (MDH, 2020)**
4-tert-Octylphenol	---	---	---	---	---	100 µg/L (HBV; MDH, 2020)	---	100	**HBV (MDH, 2020)**
Acesulfame-K	---	---	---	---	15 (WHO, 1990)	---	---	150,000	JECFA ADI (WHO, 1990)
Acetaminophen	*No values*	---	---	---	---	---	---	---	---
Albuterol	*No values*	---	---	---	---	---	---	---	---
Amoxicillin	*No values*	---	---	---	---	---	---	---	---
Atenolol	*No values*	---	---	---	---	---	---	---	---
Azithromycin	*No values*	---	---	---	---	---	---	---	---
Bisphenol A	800 (WA MTCA GWC Method B; WA DEQ, 2020); 1,800 (WA MTCA GWC Method C; WA DEQ, 2020)	0.05 (U.S. EPA, 1988a)	---	---	---	0.004 mg/kg-d (TDI; EFSA, 2017); 0.005 mg/kg-d (ADI based on NOAEL‡; FDA, 2014); 20 µg/L (nHRL-chronic; MDH, 2015)	---	20	**nHRL-chronic (MDH, 2015)**
Bromacil	---	0.1 (U.S. EPA, 1996)	---	---	---	80 µg/L (HA; U.S. EPA, 1987a)	---	80	HA (U.S. EPA, 1987a)
Butalbital	*No values*	---	---	---	---	---	---	---	---

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Caffeine	---	---	---	---	---	2.0 mg/kg-d§ (NTP CERHR, 2008); 2.5 mg/kg-d (Health Canada, 2007); 3 mg/kg-d (EFSA, 2015)	---	20,000	**CERHR ADI (NTP, 2008)**
Carbadox	*No values*	---	---	---	---	---	---	---	---
Carbamazepine	---	---	---	---	---	40 µg/L (chronic HBV; MDH, 2013b)	---	40	Chronic HBV (MDH, 2013b)
Carisoprodol	*No values*	---	---	---	---	---	---	---	---
Chloramphenicol	*No values*	---	---	---	---	---	---	---	---
Chloridazon	---	0.18 (U.S. EPA, 2005a)	---	---	---	0.1 mg/kg-d (EFSA, 2007)	---	1,000	ADI (EFSA, 2007)
Clofibric acid	*No values*	---	---	---	---	---	---	---	---
Cotinine	*No values*	---	---	---	---	---	---	---	---
Cyanazine	---	---	---	---	---	1 µg/L (HBV; MDH, 2020)	---	1.0	**HBV (MDH, 2020)**
Diaminochlorotriazine (DACT)	3 (Atrazine MCL; U.S. EPA, 2020)	---	---	100 µg/d (MADL; OEHHA, 2016)	---	---	---	3.0	**Atrazine MCL (U.S. EPA, 2020)**

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Desethylatrazine (DEA)	3 (Atrazine MCL; U.S. EPA, 2020)	---	---	100 µg/d (MADL; OEHHA, 2020b)	---	---	---	3.0	**Atrazine MCL (U.S. EPA, 2020)**
N,N-Diethyl-meta-toluamide (DEET)	---	---	1.0 (ATSDR, 2017b)	---	---	200 µg/L (HBV; MDH, 2020)	---	200	**HBV (MDH, 2020)**
Dehydronifedipine	*No values*	---	---	---	---	---	---	---	---
Diazepam	*No values*	---	---	---	---	---	---	---	---
Diclofenac	*No values*	---	---	---	---	---	---	---	---
Dilantin	*No values*	---	---	---	---	---	---	---	---
Diltiazem	*No values*	---	---	---	---	---	---	---	---
Diuron	32 (WA MTCA GWC Method B; WA DEQ, 2020); 70 (WA MTCA GWC Method C; WA DEQ, 2020)	0.002 (U.S. EPA, 1988b)	---	---	---	---	---	20	**RfD (U.S. EPA, 1988b)**
Erythromycin	*No values*	---	---	---	---	---	---	---	---
Estradiol	---	---	---	0.02 (NSRL; OEHHA, 2020c)	0.00005 (WHO, 1999)	---	39 (Cal SF; OEHHA, 2020c)	0.00026	**California SF (OEHHA, 2020c)**
Estrone	*No values*	---	---	---	---	---	---	---	---
Ethinyl estradiol - 17 alpha	---	---	---	---	---	0.0002 µg/L (chronic HBV; MDH, 2020)	---	0.0002	**Chronic HBV (MDH, 2020)**
Flumequine	*No values*	---	---	---	---	---	---	---	---

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Fluoxetine	*No values*	---	---	---	---	---	---	---	---
Gemfibrozil	*No values*	---	---	---	---	---	---	---	---
Ibuprofen	*No values*	---	---	---	---	---	---	---	---
Iohexol	*No values*	---	---	---	---	---	---	---	---
Iopromide	*No values*	---	---	---	---	---	---	---	---
Ketorolac	*No values*	---	---	---	---	---	---	---	---
Lidocaine	*No values*	---	---	---	---	---	---	---	---
Lincomycin	---	---	---	---	0.03 (WHO, 2004)	---	---	300	JECFA ADI (WHO, 2004)
Linuron	32 (WA MTCA GWC Method B; WA DEQ, 2020); 70 (WA MTCA GWC Method C; WA DEQ, 2020)	0.002 (U.S. EPA, 1987c)	---	---	---	1 µg/L (HRL; MDH, 2020)	---	1.0	**HRL (MDH, 2020)**
Lopressor	*No values*	---	---	---	---	---	---	---	---
Meclofenamic acid	*No values*	---	---	---	---	---	---	---	---
Meprobamate	*No values*	---	---	---	---	---	---	---	---
Metformin	*No values*	---	---	---	---	---	---	---	---
Methylparaben	---	---	---	---	10 (WHO, 2006)**	10 mg/kg-d (EC, 2005)**	---	100,000	JECFA ADI (WHO, 2006)
Naproxen	*No values*	---	---	---	---	---	---	---	---
Nifedipine	*No values*	---	---	---	---	---	---	---	---

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
N-Nitroso dimethylamine (NDMA)	0.002 ((WA WQS; WAC 173-200, 1990); 0.00086 (WA MTCA GWC Method B; WA DEQ, 2020); 0.0086 (WA MTCA GWC Method C; WA DEQ, 2020)	---	---	---	---	0.005 µg/L (HBV; MDH, 2020); 0.010 µg/L (NL; CalEPA, 2018); 0.30 µg/L (RL; CalEPA, 2018); 0.003 µg/L (10^{-6} level; CalEPA, 2018)	0.51 (B2)(U.S. EPA, 1987d)	0.00086	**WA MTCA GW Cleanup level Method B (WA DEQ, 2020)**
Norethisterone	*No values*	---	---	---	---	---	---	---	---
OUST (Sulfometuron methyl)	---	0.275 (U.S. EPA, 2008)	---	---	---	---	---	2,750	RfD (U.S. EPA, 2008)
Oxolinic acid	*No values*	---	---	---	---	---	---	---	---
Pentoxifylline	*No values*	---	---	---	---	---	---	---	---
Perfluoro butanoic acid (PFBA)	---	0.02 (U.S. EPA, 2014)	---	---	---	7 µg/L (HBV; MDH, 2020)	---	7.0	**HBV (MDH, 2020)**
Perfluoro octanesulfonate (PFOS)	0.07 (HA; U.S. EPA, 2016)††	---	0.000515 (ATSDR, 2018)	---	---	0.015 µg/L (HBV; MDH, 2020)	---	0.015	**HBV (MDH, 2020)**
Perfluoro octanesulfonic acid	0.07 (U.S. EPA, 2016)††	---	---	---	---	0.03 µg/L (HBV; MDH, 2020)	---	0.030	**HBV (MDH, 2020)**
Perfluoro octanoic acid (PFOA)	0.07 (U.S. EPA, 2016)††	---	---	---	---	0.035 µg/L (HBV; MDH, 2020)	---	0.035	**HBV (MDH, 2020)**

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Perfluoro-1-butanesulfonate	---	0.02 (U.S. EPA, 2014)	---	---	---	2 µg/L (HBV; MDH, 2020)	---	2.0	**HBV (MDH, 2020)**
Perfluoro-1-butanesulfonic acid	---	0.02 (U.S. EPA, 2014)	---	---	---	---	---	200	**RfD (U.S. EPA, 2014)**
Perfluoro-n-heptanoic acid	0.07 (U.S. EPA, 2016)††	---	---	---	---	---	---	0.070	**EPA HA (for PFOA + PFOS; U.S. EPA, 2016)**
Perfluoro-n-hexanoic acid	0.07 (U.S. EPA, 2016)††	---	---	---	---	---	---	0.070	**EPA HA (for PFOA + PFOS; U.S. EPA, 2016)**
Perfluoro-n-nonanoic acid	---	---	0.000003 (MRL; ATSDR, 2018)	---	---	---	---	0.030	**MRL (ATSDR, 2018)**
Perfluoropentanoic acid	0.07 (U.S. EPA, 2016)††	---	---	---	---	---	---	0.070	**EPA HA (for PFOA + PFOS; U.S. EPA, 2016)**
Primidone	*No values*	---	---	---	---	---	---	---	---
Quinoline	0.015 (WA MTCA GWC Method B; WA DEQ, 2020); 0.15 (WA MTCA GWC Method C; WA DEQ, 2020)	---	---	---	---	0.04 µg/L (HBV; MDH, 2020)	3 (U.S. EPA, 2001)	0.0033	**SF (U.S. EPA, 2001)**
Salicylic acid	*No values*	---	---	---	---	---	---	---	---

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Simazine	4 (MCL; U.S. EPA, 2020); 0.73 (WA MTCA GWC Method B; WA DEQ, 2020); 7.3 (WA MTCA GWC Method C; WA DEQ, 2020)	0.005 (U.S. EPA, 1993)	---	---	---	4 µg/L (HBV; MDH, 2020)	---	0.73	**WA MTCA GW Cleanup Level Method B (WA DEQ, 2020)**
Sucralose	---	---	---	---	15 (EC, 2000)	15 mg/kg-d (EC, 2000)	---	150,000	JECFA ADI (EC, 2000)
Sulfadiazine	*No values*	---	---	---	---	---	---	---	---
Sulfadimethoxine	*No values*	---	---	---	---	---	---	---	---
Sulfamethoxazole	---	---	---	---	---	100 µg/L (HBV; MDH, 2013a)	---	100	HBV (MDH, 2013a)
Testosterone	*No values*	---	---	---	---	---	---	---	---
Theobromine	*No values*	---	---	---	---	---	---	---	---
Theophylline	*No values*	---	---	---	---	---	---	---	---
Thiabendazole	---	0.1 (U.S. EPA, 2002)	---	---	---	---	---	1,000	RfD (U.S. EPA, 2002)
Triclosan	---	0.30 (U.S. EPA, 1998)	---	---	---	50 µg/L (HBV; MDH, 2020)	---	50	HBV (MDH, 2020)
Trimethoprim	*No values*	---	---	---	---	---	---	---	---
Tris(2-carboxyethyl)-phosphine (TCEP)	---	0.007 (U.S. EPA, 2009)	0.2 (ATSDR, 2012b)	---	---	---	0.02 (U.S. EPA, 2009)	0.50	**SF (U.S. EPA, 2009)**

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC (µg/L)	U.S. EPA RfD (mg/kg-d)	ATSDR MRL (mg/kg-d)	Cal MADL or NSRL (µg/d)	JEFCA ADI (mg/kg-d)	Other ADI or DWEL (mg/kg-d or µg/L)	Oral SF (mg/kg-d)$^{-1}$	Lowest DWEL (µg/L)*	Basis†
Tris(1-chloro-2-propyl) phosphate (TCPP)	---	0.02 (U.S. EPA, 2012c)	---	---	---	---	---	200	**RfD (U.S. EPA, 2012c)**
Tris(1,3-dichloroisopropyl) phosphate (TDCPP)	---	0.02 (U.S. EPA, 2012c)	0.02 (ATSDR, 2012b)	5.4 µg/d (NSRL; OEHHA, 2012)	---	---	---	2.0	NSRL (OEHHA, 2012)

*DWELs are calculated as follows: lowest value of identified ADIs (mg/kg-d) × 1,000 µg/mg × 10 (kg) / 1 (L/d).

†Values judged to be of sufficient quality to apply in screening-level evaluation (without further derivation of comparison levels) (see Section 4.2) are shown in bold. For all other compounds (i.e., values not bolded), further examination/ derivation of comparison levels was conducted.

‡Based on a comprehensive review of the toxicological literature, U.S. EPA identified a NOAEL for bisphenol A of 5 mg/kg-d for oral exposure (FDA, 2014). Assuming application of a 1,000-fold safety factor per the methodologies applied herein, this would be equivalent to an ADI of 0.005 mg/kg-d.

§ Per a summary published by the National Institute of Health's National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP CERHR, 2008), "The Organization of Teratology Information Services (OTIS) stated that there is no evidence that caffeine causes birth defects in humans. Groups such as OTIS and Motherisk agree that low caffeine intake (<150 mg/day or 1 ½ cups of coffee) will not likely increase a woman's chance of having a miscarriage or a low birth weight baby" (NTP CERHR, 2008). This was converted to a daily dose in mg/kg-d based on the average body weight of all pregnant women in the National Health and Nutrition Examination Survey (NHANES) of 75 kg (U.S. EPA, 2011).

**Sum of methyl, ethyl, and propyl paraben.

††Value is U.S. EPA's HA for the sum of PFOA (Perfluorooctanoic acid) + PFOS. In the absence of other data for Perfluoro-n-hexanoic acid and Perfluoropentanoic acid, it was assumed to apply to those chemicals as well.

ADI –Acceptable Daily Intake; ATSDR – Agency for Toxic Substances and Disease Registry; EC – European Commission; EFSA – European Food Safety Authority; EU – European Union Panel; HA – Health Advisory; HBV – Health Based Value; JECFA – Joint FAO/WHO Expert Committee on Food Additives; JMPR – Joint FAO/WHO Meeting on Pesticide Residues; MADL – Maximum Acceptable Dose Level for California EPA for Proposition 65; MCL – U.S. EPA Maximum Contaminant Level; MDH – Minnesota Department of Health; MRL – Minimum Risk Level from Agency for Toxic Substances and Disease Registry (ATSDR); nHRL – Noncancer Human Risk Limit; NL – Notification Level (California); NSRL – No Significant Risk Level for California EPA for Proposition 65; OEHHA – Office of Environmental Health Hazard Assessment (of California EPA); RfD – reference dose from U.S. EPA; RL – Response Level (California); SF – cancer slope factor estimated by the U.S. EPA or California EPA; TDI – Tolerable Daily Intake; WA WQS – Washington State Water Quality Standards for Ground Waters (Chapter 173-200 WAC); WHO –World Health Organization

Table B-2. Lowest Effect Doses for Noncancer Toxicity Endpoints and Corresponding Comparison Levels for Compounds Without Existing ADIs

Compound	Species/ Gender/ Study duration/ Route	Effect dose (mg/kg-d)	Effect	Reference	UF and Comparison level (µg/kg-d)
1,7-Dimethylxanthine	Human/F/Early childhood (based on data for caffeine)/ Oral	2.5 (LOAEL)	Behavioral (increased anxiety)	Nawrot et al., 2003	3,000 0.83 µg/kg-d
Acesulfame-K	Mouse/ M,F/ 4-wks/ Oral gavage	37.5 (LOAEL)	Change in gut bacterial community composition, body weight gain	Bian et al., 2017	3,000 12 µg/kg-d
Acetaminophen	Rat (F344)/ M/ 13-wks/ Oral diet	142.1 mg/kg-d (NOAEL)	Decrease in body weight, changes in serum biochemistry and absolute and relative organ weights	Toyoda et al., 2018	1,000 140 µg/kg-d
Albuterol	Mice/ F/ Gestation/ Oral	0.025 (NOAEL)	Developmental (cleft palate)	Drugs.com, 2019b	1,000 0.25 µg/kg-d
Amoxicillin	Rats/ Multi-generation/ Oral	500 (NOAEL)	Reproductive	Drugs.com, 2019d	1,000 500 µg/kg-d
Atenolol	Human/ F/ Gestation/ Oral	0.8 (LOAEL)	Developmental (decreased infant birth weights)	Bayliss et al., 2002; Lip et al., 1997; Lydakis et al., 1999	3,000 0.26 µg/kg-d
Azithromycin	Dog/ Neonatal/ Route not indicated	10 (LOAEL)	Phospholipidosis in the eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas	Pfizer, 2016	3,000 3.3 µg/kg-d
Bromacil	Mouse/ M, F/ 18-Mo/ Oral diet	40 (LOAEL)	Increased incidence of hepatocellular hypertrophy, single cell and centrilobular necrosis, hepatocellular lysis with RBC accumulation and centrilobular vacuolation.	U.S. EPA, 1996	3,000 × 10* 1.3 µg/kg-d
Butalbital	No data	---	---	---	---
Carbadox	Rat/ F/ GD8-15/ Oral gavage	10 (LOAEL)	Developmental/Reproductive (decreased maternal body weight)	Yoshimura, 2002	3,000 3.3 µg/kg-d

Compound	Species/ Gender/ Study duration/ Route	Effect dose (mg/kg-d)	Effect	Reference	UF and Comparison level (µg/kg-d)
Carbamazepine	Human/ F/ Gestation/ Oral	3 (LOAEL)	Developmental (neural tube, cardiovascular, oral clefts, urinary tract defects)	Hernandez-Diaz et al., 2000; Samren et al., 1997; Samren et al., 1999	3,000 × 10* 0.10 µg/kg-d
Carisoprodol	Rat/ M,F/ 13 wks/ Oral gavage	100 (NOAEL)	Systemic toxicity	NTP, 2000b	1,000 100 µg/kg-d
Chloramphenicol	Mice/ F/ Gestation/ Oral (drinking water)	25 (LOAEL)	Developmental (neurobehavioral deficits in pups)	IARC, 1990	3,000 × 10† 0.83 µg/kg-d
Chloridazon	Rat/ M,F/ 30-mo/ Oral diet	18 (NOAEL)	Reduced body weight gain	U.S. EPA, 2005a	1,000 18 µg/kg-d
Clofibric acid	Rat/ M,F/ Before mating through gestation/ Oral	200 (LOAEL)	Developmental/Reproductive (decreased litter size)	IARC, 1980	3,000 × 10* 6.6 µg/kg-d
Cotinine	Rat/ F/ Gestation through lactation (based on nicotine)/ Oral (drinking water)	2.4 (LOAEL)	Developmental/Reproductive (abnormal luteinizing hormone levels, delayed vaginal opening)	HSDB, 2009a	3,000 × 10† 0.080 µg/kg-d
Dehydronifedipine	Metabolite of nifedipine	See parent compound	See parent compound	See parent compound	2.0 µg/kg-d
Diazepam	Rat/ F/ Gestation/ Oral	80 (NOAEL)	Developmental/Reproductive (offspring survival)	Drugs.com, 2019g	1,000 80 µg/kg-d
Diclofenac	Mouse/ M/ 30-d/ Oral gavage	0.25 (LOAEL)	Reproductive (Reduced weights of testis, epididymis, ventral prostate and seminal vesicle; decreased sperm count, density, and motility).	Vyas et al., 2018	3,000 0.083 µg/kg-d
Dilantin	Human/ Gestation/ Oral	4.3 (LOAEL)	Developmental (congenital effects)	Hernandez-Diaz et al., 2000	3,000 × 10* 0.14 µg/kg-d
Diltiazem	Mouse, rat, rabbit/ F/ Pregnancy/ Oral	7.5 (LOAEL)	Reproductive/ developmental	Drugs.com, 2019h	3,000 2.5 µg/kg-d
Erythromycin	Rabbit/ F/ Gestation/ Oral gavage	125 (NOAEL)	Developmental	Drugs.com, 2018a	1,000 120 µg/kg-d

Compound	Species/ Gender/ Study duration/ Route	Effect dose (mg/kg-d)	Effect	Reference	UF and Comparison level (µg/kg-d)
Estrone	Human / Postmenopausal women trial/ Oral	0.004 (NOAEL)	Endocrine (evaluated several hormone and hormone binding globulin capacities)	Mashchak et al.,1982	1,000 × 10*, ‡ 0.00040 µg/kg-d
Ethinyl estradiol-17 alpha	Mice/ F/ GD10-18/ Subcutaneous (data for oral exposure not identified)	0.05 (LOAEL)	Developmental/Reproductive (increased polyovular follicles and vaginal stratification in offspring)	Kirigaya et al., 2006	3,000 × 10†, ‡ 0.0016 µg/kg-d
Flumequine	Mice/ M,F/ 90 days/ Oral	25 (NOAEL)	Systemic toxicity (hepatotoxicity)	EMEA, 1999	1,000 × 10* 2.5 µg/kg-d
Fluoxetine	Human/ F/ Gestation/ Oral	0.29 (LOAEL)	Developmental (shortened gestation, reduced birth weight, poor adaptation)	NTP, 2004	3,000 0.096 µg/kg-d
Gemfibrozil	Rat/ F/ GD15-PND21/ Oral diet	92 (LOAEL)	Developmental (reduced offspring body weights)	Fitzgerald et al., 1981	3,000 × 10* 3.0 µg/kg-d
Ibuprofen	Rat/ F/ GD21/ Oral gavage	1 (NOAEL)	Cardiovascular/ developmental	Momma and Takeuchi, 1983	1,000 1.0 µg/kg-d
Iohexol	NA (Note: compound is similar to Iopromide)	Assume same as iopromide	Assume same as iopromide	Assume same as iopromide	50 µg/kg-d
Iopromide	Human/ M,F/ PND 3-7/ Oral	150 (LOAEL)	Endocrine (higher mean thyrotropin and lower free triiodothyronine and thyroxine in infants)	Parravicini et al., 1996	3,000 50 µg/kg-d
Ketorolac	Rat/ M,F (duration not given)/ Oral	9 (NOAEL)	Reproductive (impaired fertility)	FDA, 2009	1,000 9.0 µg/kg-d
Lidocaine	Sheep/ F/ Continuous IV infusion in pregnant animals	5.8 (LOAEL)	Systemic toxicity (convulsions, hypotension, respiratory arrest, and circulatory collapse)	Morishima et al., 1990	3,000 1.9 µg/kg-d
Lincomycin	Dog/ F/ Gestation/ Parenteral	50 (NOAEL)	Developmental	Pharmacia & Upjohn, 1995	1,000 50 µg/kg-d
Lopressor	Rat/ M/ 60-d/ Oral	3.5 (LOAEL)	Reproductive (Decrease in sperm motility)	el-Sayed et al., 1998	3,000 1.1 µg/kg-d

Compound	Species/ Gender/ Study duration/ Route	Effect dose (mg/kg-d)	Effect	Reference	UF and Comparison level (µg/kg-d)
Meclofenamic acid	Rat/ M,F/ Multigenerational/ Oral	3 (NOAEL)	Developmental/Reproductive (prolonged gestation, decreased weanling weights, and increased weanling mortality)	Petrere et al., 1985	1,000 3.0 µg/kg-d
Meprobamate	Rat/ M,F/ Gestation/ Oral gavage	32 (LOAEL)	Developmental (increased activity in offspring)	Caldwell and Spille, 1964	3,000 10 µg/kg-d
Metformin	Rat/ M, F/ 13 weeks/ Oral gavage	200 (NOAEL)	Decreased body weight, metabolic acidosis	Quaile et al., 2010	1,000 200 µg/kg-d
Methylparaben	Rat and mice/ M, F/ GD 6-18/ Oral	550 (NOAEL)	Developmental (no evidence of effects on implantation, resorption, or fetuses)	Food Drug and Research Labs, Inc., 1972 as cited in U.S. EPA, 2005b	1,000 550 µg/kg-d
Naproxen	Rat & Rabbit/ Gestation/ Route not indicated	20 (NOAEL)	Reproductive/ Developmental (no evidence of impaired fertility or harm to fetus)	Roche, 2012	1,000 20 µg/kg-d
Nifedipine	Rat, mouse, rabbit/ Developmental studies/ Route not indicated	6 (LOAEL)	Developmental/Reproductive (teratogenic, embryotoxic, or fetotoxic effects)	HSDB, 2010	3,000 2.0 µg/kg-d
Norethisterone	Mouse/ F / GD 8-15/ Oral	10 (LOAEL)	Developmental (embryolethality)	IARC, 1979	3,000 × 10*,‡ 0.33 µg/kg-d
OUST (Sulfometuron methyl)	Rabbit/ F/ Gestation/ Oral gavage	30 (NOAEL)	Developmental (fused sternebrae)	Hazelton Laboratories America, Inc., 1990 as cited in CalEPA, 2002	1,000 30 µg/kg-d
Oxolinic acid	Rat/ M, F/ 104-wk/ Oral diet	10.9 (NOAEL)	Reproductive (benign Leydig cell tumors of testis in males)	Yamada et al., 1994	1,000 11 µg/kg-d
Pentoxifylline	Mouse/ Before mating and during the first 7 days or GD6-15/ Oral	50 (NOAEL)	Reproductive	Shepard and Lermire, 2004	1,000 × 10† 5.0 µg/kg-d
Primidone	Rat/ F/ GD 8-17/ Oral gavage	40 (NOAEL)	Developmental/Neurobehavioral (deficits in neurobehavioral tests)	Pizzi et al.,1996	1,000 × 10* 4.0 µg/kg-d
Salicylic acid	Rat/ F/ GD 20-21/ Oral	20 (LOAEL)	Developmental/Reproductive (increased time to parturition, bleeding during parturition)	HSDB, 2009b	3,000 6.6 µg/kg-d

Compound	Species/ Gender/ Study duration/ Route	Effect dose (mg/kg-d)	Effect	Reference	UF and Comparison level (µg/kg-d)
Sucralose	Mouse/ M, F/ 2 yr/ Oral diet	1,500 (NOAEL)	Decreased peripheral blood erythrocyte counts in females.	Berry et al., 2016	1,000 × 10* 150 µg/kg-d
Sulfadiazine	Dog/ 28-d/ Oral	12.5 (NOAEL)	Systemic toxicity (hypothyroidism)	Panciera and Post, 1992	1,000 12 µg/kg-d
Sulfadimethoxine	Dog/ 13-wk/ Oral	160 (NOAEL)	No effect	Zoetis, 2016	1,000 160 µg/kg-d
Sulfamethoxazole	Rat/ F/ Gestation/ Route not reported	512 (NOAEL, in combination w/ 128 mg/kg-d trimethoprim)	Teratology	Monarch Pharmaceuticals, No date	1,000 × 10* 51 µg/kg-d
Testosterone	Rat/ F/ GD5-11	4 (LOAEL)	Reproductive/developmental (prevention of implantation, fetal loss, delayed parturition)	IARC, 1979	3,000 × 10†, ‡ 0.13 µg/kg-d
Theobromine	Mouse/ F/ Gestation through lactation/ Oral	2 (LOAEL)	Developmental/Reproductive (decreased weight and immune function on offspring)	Chorostowska-Wynimko et al., 2004	3,000 0.66 µg/kg-d
Theophylline	Mouse/ M,F/ 14-week continuous breeding study/ Oral	120 (LOAEL)	Developmental/Reproductive (litter size, pup mortality)	Drugs.com, 2018c	3,000 40 µg/kg-d
Thiabendazole	Mouse/ F/ GD6-15/ Oral	25 (NOAEL)	Systemic toxicity (decreases in maternal weight gain)	Lankas et al., 2001	1,000 25 µg/kg-d
Triclosan	Rat/ F/ 8 months/ Oral gavage	2.35 (NOAEL)	Decrease in thyroxine (T_4) levels	Louis et al., 2017	1,000 × 10* 0.23 µg/kg-d
Trimethoprim	Rat/ M, F/ Oral	14 (NOAEL)	Fertility/reproduction	Pfizer, 2018	1,000 × 10† 1.4 µg/kg-d

*Additional UF of 10 was applied because compound shows evidence of being a nongenotoxic carcinogen (see Table B-4). If a substance was determined to have more than one special characteristics (e.g., a nongenotoxic carcinogen and an EDC), only one factor of 10 was applied.
†Additional UF of 10 was applied because compound shows evidence of genotoxicity (see Table B-4). If a substance was determined to have more than one special characteristics (e.g., genotoxic carcinogen and an EDC), only one factor of 10 was applied.
‡Additional UF of 10 was applied because the compound is a purported EDC. If a substance was determined to have more than one special characteristics (e.g., a nongenotoxic carcinogen and an EDC), only one factor of 10 was applied.
ADI – Acceptable Daily Intake; F – female; GD – gestation day; LOAEL – lowest observed adverse effect level; M – male; NOAEL – no observed adverse effect level; PND – postnatal day; UF – uncertainty factor

Table B-3. Lowest Therapeutic Doses for Pharmaceutical Compounds and Corresponding Comparison Levels

Compound	Lowest therapeutic dose (mg/d)	Treatment endpoint	Age group and assumed body weight (kg)	Minimum therapeutic dose (µg/kg-d)	Pregnancy category & adverse effects	UF and Comparison level (µg/kg-d)
Acetaminophen	650	Pain relief	Adult, 80	8,125	Not reported	3,000 × 10* 0.27 µg/kg-d
Albuterol	0.18	Reversible obstructive airway disease	Adult, 80	2	C	3,000 0.00075 µg/kg-d
Amoxicillin	750	Ear/nose/throat infection	Adult, 80	9,375	B	3,000 3.1 µg/kg-d
Atenolol	25	Hypertension	Adult, 80	313	D (low birth weight)	3,000 0.10 µg/kg-d
Azithromycin	600	Infections caused by Mycobacterium avium complex	Adult, 80	7,500	B	3,000 2.5 µg/kg-d
Butalbitol	50	Tension headache	Adult, 80	625	C (seizure)	3,000 0.20 µg/kg-d
Carbadox	Veterinary use	Veterinary use	---	---	---	---
Carbamazepine	10	Epilepsy	Child <6, 10	1,000	D (developmental delays, congenital abnormalities); severe and sometimes fatal dermatologic reactions	3,000 × 10† 0.033 µg/kg-d
Carisoprodol	250	Muscle relaxant	Adult, 80	3,125	C (adverse effects on fetal growth and postnatal survival)	3,000 1.0 µg/kg-d
Chloramphenicol	1	Antibiotic	Adult, 80	13	C (early embryonic resorptions in animals)	3,000 × 10* 0.00041 µg/kg-d
Clofibric acid	2000	Antilipidemic	Adult, 80	25,000	C (increased mortality)	3,000 × 10† 0.83 µg/kg-d

Compound	Lowest therapeutic dose (mg/d)	Treatment endpoint	Age group and assumed body weight (kg)	Minimum therapeutic dose (µg/kg-d)	Pregnancy category & adverse effects	UF and Comparison level (µg/kg-d)
Dehydronifedipine	Metabolite of nifedipine	See parent compound	See parent compound	375	See parent compound	3,000 0.12 µg/kg-d
Diazepam	2	Antianxiety	Adult, 80	25	D (congenital abnormalities, neonatal respiratory and feeding difficulties)	3,000 0.0083 µg/kg-d
Diclofenac	100	Pain relief	Adult, 80	1,250	C (ductus arteriosus defects)	3,000 0.41 µg/kg-d
Dilantin	300	Epilepsy	Adult, 80	3,750	D (congenital abnormalities)	3,000 × 10† 0.12 µg/kg-d
Diltiazem	120	Anti-hypertensive	Adult, 80	1,500	C	3,000 0.50 µg/kg-d
Erythromycin	300	Antibiotic	Pediatric, 10	30,000	B	3,000 10 µg/kg-d
Estrone	0.014 (injected)	Ovary problems (female hypogonadism or failure or removal of both ovaries)	Adult, 80	0.175	X (Increased risk of myocardial infarction and stroke, endometrial cancer, breast cancer)	3,000 × 10†, ‡ 0.0000058 µg/kg-d
Ethinyl estradiol - 17 alpha	0.02	Hormone replacement therapy	Adult, 80	0.25	X (Increased risk of thromboembolism, myocardial infarction and stroke, endometrial cancer, breast cancer)	3,000 × 10*, ‡ 0.0000083 µg/kg-d
Flumequine	Removed from clinical use	Antibiotic	---	---	---	---
Fluoxetine	10	Depression, obsessive compulsive disorder	Pediatric (children & adolescents), 30	333	C (shortened gestation, reduced birth weight, poor neonatal adaptation)	3,000 0.11 µg/kg-d
Gemfibrozil	1,200	Lipid regulation	Adult, 80	15,000	C (gall bladder disease)	3,000 × 10† 0.50 µg/kg-d

Compound	Lowest therapeutic dose (mg/d)	Treatment endpoint	Age group and assumed body weight (kg)	Minimum therapeutic dose (µg/kg-d)	Pregnancy category & adverse effects	UF and Comparison level (µg/kg-d)
Ibuprofen	200	Pain relief	Adult, 80	2,500	C	3,000 0.83 µg/kg-d
Ketorolac	40	Pain relief	Adult, 80	500	C (no evidence of reproductive effects in animals)	3,000 0.16 µg/kg-d
Lidocaine	90	Anesthesia	Child, 30	3,000	B (no evidence of harm to fetus in studies in rats)	3,000 1.0 µg/kg-d
Lincomycin	100	Antibiotic	Pediatric, 10	10,000	C	3,000 3.3 µg/kg-d
Lopressor	25	Antihypertensive	Adult, 80	313	C (decreased neonatal survival)	3,000 0.10 µg/kg-d
Meclofenamic acid	2,000	Pain relief	Adult, 80	25,000	C (no evidence of reproductive effects in animals)	3,000 8.3 µg/kg-d
Meprobamate	200	Anxiety	Child, 30	6,667	NA (congenital malformations)	3,000 2.2 µg/kg-d
Metformin	1000	Type 2 diabetes	Adult, 80	12,500	B	3,000 4.1 µg/kg-d
Naproxen	125	Juvenile arthritis	Child, 30	4,167	B (premature closure of ductus arteriosus)	3,000 1.3 µg/kg-d
Nifedipine	30	Anti-anginal	Adult, 80	375	C (congenital abnormalities)	3,000 0.12 µg/kg-d
Norethisterone	0.35 (oral)	Oral contraceptive	Adult, 80	4	X (vaginal adenosis, squamous cell dysplasia of the uterine cervix, and vaginal cancer development in female offspring and an increased risk of urogenital abnormalities and testicular cancer in male offspring)	3,000 × 10†,‡ 0.00014 µg/kg-d
Oxolinic acid	Veterinary use	Veterinary use	---	---	---	---
Pentoxifylline	800	Blood viscosity-reducing agent	Adult, 80	10,000	C	3,000 × 10* 0.33 µg/kg-d

Compound	Lowest therapeutic dose (mg/d)	Treatment endpoint	Age group and assumed body weight (kg)	Minimum therapeutic dose (µg/kg-d)	Pregnancy category & adverse effects	UF and Comparison level (µg/kg-d)
Primidone	100	Anticonvulsant	Adult, 80	1,250	NA	3,000 × 10† 0.041 µg/kg-d
Salicylic acid	325 (based on acetyl salicylic acid)	Pain relief	Adult, 80	4,063	D	3,000 1.3 µg/kg-d
Sulfadiazine	1,000	Rheumatic fever prophylaxis	Adult, 80	12,500	C (neonatal jaundice and kernicterus)	3,000 4.1 µg/kg-d
Sulfadimethoxine	Veterinary use	Veterinary use	---	---	---	---
Sulfamethoxazole	480	Urinary tract infection	Child (>2 months), 30	16,000	C	3,000 × 10† 0.53 µg/kg-d
Testosterone	50 (topical)	Replacement therapy in adult males for deficiency or absence of endogenous testosterone	Adult, 80	625	X (teratogenic)	3,000 × 10*,‡ 0.020 µg/kg-d
Theophylline	2	Bronchodilator	Pediatric, 10	200	C	3,000 0.066 µg/kg-d
Trimethoprim	80	Urinary tract infection	Pediatric, 10	8,000	C	3,000* 0.26 µg/kg-d

Source: RxList.com, 2019e

*Additional UF of 10 was applied because compound shows evidence of genotoxicity (see Table B-4). If a substance was determined to have more than one special characteristics (e.g., genotoxic carcinogen and an EDC), only one factor of 10 was applied.

†Additional UF of 10 was applied because compound shows evidence of being a nongenotoxic carcinogen (see Table B-4). If a substance was determined to have more than one special characteristics (e.g., genotoxic carcinogen and an EDC), only one factor of 10 was applied.

‡Additional UF of 10 was applied because the compound is a purported EDC. If a substance was determined to have more than one special characteristics (e.g., genotoxic carcinogen and an EDC), only one factor of 10 was applied.

ADHD – Attention deficit hyperactivity disorder; NA – Not available; UF – Uncertainty factor

Table B-4. Carcinogenicity and Genotoxicity Data and Corresponding Comparison Levels for Compounds Without Existing ADIs

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
1,7-Dimethylxanthine	*Assume same as caffeine (caffeine metabolite)*	Mixed	Not applicable (no increase in tumor incidence)	---	---
Acesulfame-K	No increase in tumor incidence in male and female mice administered acesulfame-K in diet at 0, 3,000, 10,000, or 30,000 ppm for 80 weeks (Beems 1991 as cited in CPDB, 2007c). No increase in tumor incidence in male and female rats administered acesulfame-K in diet at 0, 3,000, 10,000, or 30,000 ppm for 113 weeks (Sinkeldam et al., 1991 as cited in CCRIS, 2009a).	Mixed [Negative in *in vitro* mouse lymphoma assay; negative in females and positive in males in *in vivo* mouse bone marrow micronucleus assay) (CCRIS, 2009a).]	Not applicable (no increase in tumor incidence)	---	---
Acetaminophen	Increased incidence of liver tumors in oral dietary studies in male and female mice (70 weeks to 2 years) and male and female rats (78 weeks to 2 years) (CPDB, 2019; Flaks et al., 1985). Classified by IARC (1999) as Group 3, unclassifiable as to its carcinogenicity in humans.	Positive (characterized by IARC (1999) as "Overall, paracetamol was genotoxic in mammalian cells *in vivo* and *in vitro*) [Negative in multiple *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, TA97A, 98, 100, 102, 1535, 1537, 1538 w/ and w/o metabolic activation. Positive in one assay in TA100 w/ activation. Positive in *in vitro* micronucleus assay in rat kidney fibroblasts w/o activation and in CHL cells w/o activation) (CCRIS, 2010a).]	Flaks et al., 1985; 18 months, rat (M, F); liver neoplastic nodules 0 mg/kg-d = 0/40 250 mg/kg-d = 0/49 500 mg/kg-d = 10/50	0.002	0.50
Albuterol	Dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year oral study in rats (Jack et al., 1983.)	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, TA98, 1537, 1538 w/ and w/o metabolic activation or in *E. coli* WP2, WP2uvrA, or WP67) (HSDB, 2005a).]	Not applicable (no increase in malignant tumor incidence)	---	---
Amoxicillin	Long-term studies in animals have not been performed to evaluate carcinogenic potential (Drugs.com, 2019d).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium* (HSDB, 2017a).]	Not applicable (no data)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Atenolol	In a two-year oral rat study, increase in benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males receiving 500-1,500 but not 300 mg/kg-d of atenolol (HSDB, 2003a).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, TA98, 100, 1535, 1537 w/ and w/o metabolic activation) (CCRIS, 2006a). Negative *in vitro* in rat and human hepatocytes (CCRIS, 2006a).]	Not applicable (data not located; based on negative mutagenicity data, mechanism for development of cancers in rodents likely to be nongenotoxic)	---	---
Azithromycin	No studies identified.	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains TA98, 100, 1535, 1537, w/ and w/o metabolic activation and in *in vitro* assay in mouse lymphoma cells w/ and w/o metabolic activation (CCRIS, 1995).]	Not applicable (no data)	---	---
Bromacil	No increase in tumor incidence in 2-year oral dietary study in rats at doses up to 2,500 ppm. Significant increase in combined hepatocellular adenomas and carcinomas at highest dose in 18-mo oral dietary study in mice with doses up to 5,000 ppm (CCRIS, 2007).	Negative [Negative in *in vitro* bacterial reverse mutagenicity in *S. typhimurium*, including strains TA97, 98, 100, 1535, 1537, 1538 w/ and w/o metabolic activation in *E. Coli* WP2 w/ and w/o metabolic activation. Positive *in vitro* in mouse lymphoma cells and in human peripheral blood lymphocytes (but at an extremely high dose). Negative *in vitro* in CHO/HPRT assays (CalEPA, 1997).]	Not applicable (data not located; based on negative mutagenicity data, mechanism for development of cancers in rodents likely to be nongenotoxic)	---	---
Butalbital	No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis (Drugs.com, 2019c).	No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis (Drugs.com, 2019c).	Not applicable (no data)	---	---
Caffeine	No increase in tumor incidence in multiple long-term oral studies in mice and rats. Negative in male and female mice at 55 mg/kg-d via diet for 77 weeks and negative in female mice at 100 mg/kg-d via water for 24 months. In female rats, negative via water at 57.1 mg/kg-d for 54 weeks, via gavage at 71.4 mg/kg-d for 24 months, via water at 11.4,	Mixed [Negative in *in vitro* bacterial reverse mutagenicity in *S. typhimurium*, strains TA98, 100, 1535, 1537, 1538, w/ and w/o metabolic activation and in *E. Coli* WP2 w/ and w/o metabolic activation. Positive in *in vitro* micronucleus assay in rat kidney cells and in mouse lymphoma cells w/ and w/o metabolic activation. Positive in *in vivo*	Not applicable (no increase in tumor incidence)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
	24.6, 53.1, or 114 mg/kg-d for 24 months, and via water at 42.9 or 85.7 mg/kg-d for 24 months. In male rats, negative via gavage at 71.4 mg/kg-d for 24 months, via diet at 40.8 mg/kg-d for 25 months, via water at 10, 21.5, 46.5, or 100 mg/kg-d for 24 months, via diet at 40.8 mg/kg-d for 88 weeks, and via water at 37.5 or 75.0 mg/kg-d for 24 months (CPDB, 2007b). IARC identified caffeine as Group 3: not classifiable as to its carcinogenicity in humans based on inadequate evidence for carcinogenicity in humans and experimental animals (IARC, 1991).	chromosomal aberration assay but negative in *in vivo* micronucleus assay in mouse bone marrow (CCRIS, 2010b).]			
Carbadox	Increase in benign nodular hyperplasia in the liver of rats administered orally for two years (Stebbins and Coleman, 1967).	Positive but limited [Chromosomal damage in human lymphocytes *in vitro* (HSDB, 2017b).]	Not applicable (no increase in malignant tumor incidence)	---	---
Carbamazepine	Increase in liver carcinomas in female rats administered 25, 75, or 250 mg/kg-d orally in the diet for 2-years (Novartis, 2010; Singh et al., 2005).	Negative [Negative findings in bacterial and mammalian mutagenicity studies (RxList.com, 2019c).]	Not applicable (data not located; based on negative mutagenicity data, mechanism for development of cancers in rodents likely to be nongenotoxic)	---	---
Carisoprodol	No evidence of carcinogenicity in dietary studies in rats (1 year) or dogs (6 months) (Berger et al., 1959).	Negative [Negative in *in vitro* bacterial reverse mutagenicity in *S. typhimurium*, strains TA98, 100, 1535, 1537, w/ and w/o metabolic activation (CCRIS, 1993)].	Not applicable (no increase in tumor incidence)	---	---
Chloramphenicol	Induces aplastic anemia in humans, and this condition is related to the occurrence of leukemia; probably carcinogenic to humans (Group 2A) (IARC, 1990). Inadequate testing in animals.	Mixed [Negative in *in vitro* bacterial reverse mutagenicity in *S. typhimurium* w/ and w/o metabolic activation. Positive *in vitro* in CHL cells w/ but not w/o activation. Negative *in vitro* for SCEs in human leukocytes, but positive increase in chromosomal aberrations (CCRIS, 1992a; HSDB, 2018).]	Not available (no data on tumor incidence located). **Use VSD approach to calculate comparison level (see Table 4-5)**	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Chloridazon	No increase in tumor incidence in 30-mo oral dietary study in rats at doses up to 2,000 ppm, or in 96-wk oral dietary study in mice at doses up to 20,000 ppm, or in 24-mo oral dietary study in mice at doses up to 5,000 ppm (CalEPA, 2000).	Negative [Negative in *in vitro* bacterial reverse mutagenicity *in S. typhimurium*, strains TA98, 100, 1535, 1537, w/ and w/o metabolic activation, and in *E. coli* WP2 uvrA, w/ and w/o metabolic activation. Negative *in vitro* for unscheduled DNA synthesis in rat primary hepatocytes. Negative *in vivo* for chromosomal aberrations in mice (CalEPA, 2000)].	Not applicable (no increase in tumor incidence)	---	---
Clofibric acid	Increased incidence of hepatocellular carcinoma and acinar-cell carcinoma in rats administered in diet at 0.5% (w/v) for 28 months (Reddy and Qureshi, 1979), but no increased cancer risk reported in humans with long-term therapeutic administration (Gonzalez et al., 1988). Demonstrated to be a peroxisome proliferator in rodents, with mechanism of action for carcinogenicity not relevant to humans. Classified as Group 3, not classifiable as to carcinogenicity in humans, by IARC (1996a).	Negative [Negative in *in vitro* bacterial reverse mutagenicity *in S. typhimurium*, strains TA100, 102, 2638, w/ and w/o metabolic activation, and in *E. coli* WP2 uvrA. Negative *in vitro* in Chinese hamster liver cells and mixed in mouse lymphoma cells (CCRIS, 2009b).]	Not applicable (based on negative mutagenicity data, mechanism for development of cancers in rodents likely to be nongenotoxic)	---	---
Cotinine	Metabolite of nicotine. No increase in tumor incidence was seen female rats administered nicotine via inhalation at an average concentration of 0.5 mg/m3 for 20 hours per day, 5 days/week for 103 weeks (HCN, 2005).	Negative [Negative in *in vitro* bacterial reverse mutagenicity in *S. typhimurium*, strains TA98, 100, 1535, 1537, 1538 w/ and w/o metabolic activation (CCRIS, 1997).]	Not applicable (no increase in tumor incidence)	---	---
DEET	Negative in long-term oral studies in dogs, rats, and mice (dogs dosed by capsule up to 400 mg/kg-d for 52 weeks; male rats dosed up to 100 mg/kg-d and female rats dosed up to 400 mg/kg-d via diet for 2-yrs; and male and female mice dosed up to 1,000 mg/kg-d via diet for 78 weeks) (ATSDR, 2017b).	Predominantly negative [Negative in *in vitro* bacterial reverse mutagenicity assays in *S. typhimurium*, strains TA97, 98, 100, 1535, 1537, and 1538, w/ and w/o metabolic activation. Negative *in vitro* in chromosomal aberration assay in CHO cells w/ and w/o metabolic activation and unscheduled DNA synthesis assay in rat hepatocytes w/o activation. Positive in *in vitro* assay in cultured primary human nasal mucosal cell assay w/activation (ATSDR, 2017b).]	Not applicable (no increase in tumor incidence)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Dehydronifedipine	Metabolite of nifedipine	See parent compound	See parent compound	See parent compound	---
Diazepam	No increase in incidence of tumors in both mice and rats administered in diet for 80 weeks or 24 months (CPDB, 2007d). Classified as Group 3, not classifiable as to its carcinogenicity in humans, by IARC (HSDB, 2011).	Mixed [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains TA97, 98, 100, 1535, 1537, 1538, w/ and w/o metabolic activation thought reportedly positive in another test in strain TA100. Negative in *in vitro* chromosomal aberration assay in CHL cells thought reportedly positive in a bone marrow micronucleus test. Negative for chromosomal aberrations in human lymphocytes *in vivo* (CCRIS, 2006b; HSDB, 2011).]	Not applicable (no increase in tumor incidence)	---	---
Diclofenac	No evidence of carcinogenicity in long-term studies in mice (Micromedex Thomson Health Care, 2006)	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains TA98, 1537, 1538, w/ and w/o metabolic activation and in *E. coli* WP2 uvr$^-$ w/ and w/o metabolic activation (Kadotani et al., 1984). Negative in *in vitro* chromosomal aberration assay and in *in vivo* micronucleus assay in mouse bone marrow (EMA, 2003).]	Not applicable (no increase in tumor incidence)	---	---
Dilantin	Increase in liver neoplasms in female mice and male rats administered orally for 2-years (NTP, 1993). Classified by IARC as Group 2B, possibly carcinogenic to humans (IARC, 1996c) and as Reasonably anticipated to be a human carcinogen by NTP (1993).	Negative, although IARC (1996c) suggests evidence is mixed [Negative in multiple *in vitro* bacterial reverse mutagenicity assays in *S. typhimurium*, strains TA97, 98, 100, 1530, 1535, 1537, w/ and w/o metabolic activation. Negative *in vitro* in mouse lymphoma cells w/ and w/o activation and in CHO cells. Negative in in vivo micronucleus assays in mice (CCRIS, 2008)].	NTP, 1993: 2 yr, mouse (F); liver adenomas and carcinomas in females 0 mg/kg-d = 5/48 50 mg/kg-d = 14/49 160 mg/kg-d = 30/50	0.0012	0.83
Diltiazem	A 24-month oral study in rats and a 21-month oral study in mice showed no evidence of carcinogenicity (Drugs.com, 2019h).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium* and in vitro and *in vivo* in mammalian cell assays (HSDB, 2003b).]	Not applicable (no increase in tumor incidence)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Erythromycin	Long-term oral dietary studies conducted with erythromycin stearate in rats and mice did not provide evidence of tumorigenicity (Drugs.com, 2018a).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains TA98, 100 (CCRIS, 2006c).]	Not applicable (no increase in tumor incidence)	---	---
Estrone	Identified as reasonably anticipated to be a human carcinogen by NTP, based on sufficient evidence of carcinogenicity in experimental animals—when administered orally, topically, subcutaneously, or by implantation, estrone induced and increased incidence of mammary tumors in mice, and when administered subcutaneously or by implantation, it induced an increased incidence of pituitary, adrenal, mammary, and bladder tumors in rats. When administered subcutaneously, estrone caused kidney tumors in both castrated and intact male hamsters, and pituitary. Identified as having sufficient evidence for carcinogenicity to animals by IARC (1987) based on the same evidence as above.	Negative [Not mutagenic to Chinese hamster cells *in vitro* (IARC, 1987).]	Not applicable (tumor incidence data not located)	---	---
Ethinyl estradiol-17 alpha	One study found increases in liver tumors in female rats administered a dose of 0.429 mg/kg-d via gavage for 52 weeks (CPDB, 2007f). Listed as a Proposition 65 carcinogen in California. NTP concludes that it is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in animals (NTP, 2000c).	Positive [Positive for chromosomal aberrations in human blood lymphocytes and in CHO cells *in vitro*, and mixed results for chromosomal aberrations in mouse bone marrow cells *in vivo* (CCRIS, 2011).]	CPDB, 2007f: 1yr, rat (F), liver tumors; 0 mg/kg-d = 0/8 0.429 mg/kg-d = 4/13	0.19	0.0052
Flumequine	Increased incidence of liver tumors in mice (EMEA, 1999), but mechanism of carcinogenicity thought to be nongenotoxic and not relevant to humans (HSDB, 2017c).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, and in HGPRT test, gene mutation assay, and chromosomal aberration assay (HSDB, 2017c).]	Not applicable (based on negative mutagenicity data, mechanism for development of cancers in rodents likely to be nongenotoxic)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Fluoxetine	No evidence of carcinogenicity in 2-yr oral dietary studies of mice and rats at doses up to 12 mg/kg-d for male mice, 13 mg/kg-d for female mice, 8 mg/kg-d for male rats, and 10 mg/kg-d for female rats (Bendele et al. 1992)	Negative [In *in vitro* tests, fluoxetine hydrochloride was negative for in the bacterial reverse mutagenicity assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay. It was also negative in an *in vivo* SCE assay in Chinese hamster bone marrow cells (HSDB, 2005b).]	Not applicable (no increase in tumor incidence)	---	---
Gemfibrozil	Increased adrenal, pancreatic, liver, and testes tumors in male rats administered 0, 30, or 300 mg/kg-d in diet for 2 years (Fitzgerald et al. 1981). No increase in tumor incidence in females. In mice administered same doses, increase in liver tumors at mid but not high dose in males; no increases in tumor incidence in females. Gemfibrozil causes proliferation of peroxisomes in rat liver, a mechanism that is not operative in humans. In a clinical trial in Finland, no difference was found in cancer incidence or mortality between the treated (n = 2859) and control groups followed for 5 years (IARC, 1996b). IARC classified it as Group 3: Not classifiable as to its carcinogenicity in humans based on inadequate evidence in humans and limited evidence in experimental animals (IARC, 1996b).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium* strains 98, 100, 1535, 1537, 1538 w/ and w/o metabolic activation (IARC, 1996b).]	Fitzgerald et al., 1981: 2 yr, rat (M); Interstitial cell tumors of the testes 0 mg/kg-d = 1/50 30 mg/kg-d = 8/50 300 = 17/50 Mechanism for development of cancers in rodents not likely to be relevant to humans.	---	---
Ibuprofen	No increased incidence of tumors in mice or rats of either sex given the drug in diet for 43 or 56 weeks (Adams et al., 1970).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium* strains 97A, 98, 100, 102, 1535, 1537, 1538 w/ and w/o metabolic activation (CCRIS, 2000).]	Not applicable (no increase in tumor incidence)	---	---
Iohexol	Long-term animal studies have not been conducted.	No data	Not applicable (no data)	---	---
Iopromide	Long-term animal studies have not been conducted.	No data	Not applicable (no data)	---	---
Ketorolac	Long-term animal studies have not been conducted.	No data	Not applicable (no data)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Lidocaine	Not carcinogenic when administered topically weekly to dorsal skin of mice for 26 weeks (HSDB, 2015). No oral studies identified.	Negative [Negative in wing somatic mutation and recombination tests in *Drosophila melanogaster* (HSDB, 2015).]	Not applicable (no data)	---	---
Lincomycin	In a 26-month study in pregnant rats and offspring, administration in feed at doses up to 100 mg/kg-d did not result in an increase in tumor incidence (WHO, 2000). Not listed as carcinogenic by IARC, NTP or OSHA (Pharmacia & Upjohn 1995).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium* w/ and w/o metabolic activation, HGPRT assay in CHL cells, and chromosomal aberration assays in CHL cells and human lymphocytes. Positive *in vitro* for UDS in rat hepatocytes. Negative *in vivo* in rat and mouse micronucleus assays (HSDB, 2013). WHO (2000) concludes that the weight of evidence suggests non-genotoxic.]	Not applicable (no increase in tumor incidence)	---	---
Lopressor	Increased incidence of benign lung tumors in female mice administered it orally for up to 21 months. No increase in neoplasms in rats administered orally for 2 years (McEvoy, 2003).	Negative [Negative in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains 98, 100, 1535, 1537, w/ and w/o metabolic activation. Negative *in vitro* for UDS in rat and human hepatocytes (CCRIS, 2006d).]	Not applicable (no increase in malignant tumor incidence)	---	---
Meclofenamic acid	An 18-month study in rats revealed no evidence of carcinogenicity (Drugs.com, 2019a)	No data	Not applicable (no increase in tumor incidence)	---	---
Meprobamate	Long-term animal studies have not been conducted.	No data	Not applicable (no data)	---	---
Metformin	In long-term oral carcinogenicity studies (104 weeks in rats and 91 weeks in mice), increased incidence of benign stromal uterine polyps in female rats and no evidence of carcinogenicity in other groups (RxList.com, 2019d).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA98 and 100 w/ and w/o metabolic activation and in Comet assay for DNA fragmentation (Ullah et al., 2016). Negative *in vitro* for chromosomal aberrations and in micronuclei tests in human lymphocyte cultures (Sant'Anna et al., 2013). Negative *in vivo* in mouse micronucleus assay (CCRIS, 2009c).]	Not applicable (no increase in malignant tumor incidence)	---	---
Methylparaben	No indication of increase in tumor incidence in 96-wk dietary study in rats at doses up to	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S.*	Not applicable (no increase in tumor	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
	5,900 mg/kg-d (U.S. EPA, 2005b).	*typhimurium* strains TA98, 100, 1537, 1538 w/ and w/o metabolic activation, and in E. coli strain WP2 (CCRIS, 1992b).]	incidence)		
Naproxen	No evidence of carcinogenicity in 2-yr oral study in rats (Roche, 2012).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA97A, 98, 100, 102, 1537, 1538, w/ and w/o metabolic activation, and in *E. coli* WP2 uvrA (CCRIS, 2001a).]	Not applicable (no increase in tumor incidence)	---	---
Nifedipine	No evidence of carcinogenicity in long-term studies in rats (RxList.com, 2019a).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA97, 98, 100, 1535, w/ and w/o metabolic activation (CCRIS, 1994).]	Not applicable (no increase in tumor incidence)	---	---
Norethisterone	Increased incidence of liver and lung tumors in chronic oral studies in mice and in mammary tumors in rats (IARC, 1979). Classified as reasonably anticipated to be a carcinogen in humans by NTP based on studies in animals (NTP, 2016).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA97, 98, 100, 1535, 1537, 1538 w/ and w/o metabolic activation and in *E. coli* WP2 uvrA. Negative for chromosomal aberrations in human lymphocytes in vitro and in an in vivo micronucleus assay in rats (CCRIS, 2006e).]	Not applicable (despite investigation by IARC, NTP, and CalEPA, no CSFs have been derived)	---	---
OUST (Sulfometuron methyl)	No evidence of increased tumor incidence in 2-yr oral feeding study in rats at doses up to 199 mg/kg-d in males and 260 mg/kg-d in females or in 18-mo oral feeding study in mice at doses up to 5,000 ppm (CalEPA, 2002).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strain TA98, 100, 1535, 1537, w/ and w/o metabolic activation. Negative *in vitro* for mutagenicity in CHO cells or for unscheduled DNA synthesis in rat hepatocytes (CalEPA, 2002).]	Not applicable (no increase in tumor incidence)	---	---
Oxolinic acid	Increased incidence of benign Leydig cell tumors of the testes in male rats administered orally in the diet for 2 years. No increase in tumor incidence in female rats or male or female mice (CCRIS, 2001b).	Positive [Positive *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strain TA102 and 2638 w/o metabolic activation and in E. coli WP2 w/o activation (CCRIS, 2001b).]	Not applicable (no increase in malignant tumor incidence)	---	---
Pentoxifylline	Statistically significant increase in benign mammary fibroadenomas in female rats (Drugs.com, 2019e).	Positive [Positive for chromosomal aberrations in vitro in CHL cells and in human lymphocytes (CCRIS, 2005)].	Not applicable (no increase in malignant tumor incidence,	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
			however, shows evidence of genotoxicity) **Use VSD approach to calculate comparison level (see Table 4-5)**		
Primidone	Increased incidence of liver tumors in 2-year oral study in male and female mice (CPDB, 2007e). Per IARC, "The reported carcinogenicity of primidone in mice is likely to be mediated through a non-genotoxic mechanism resulting from the metabolism of primidone to phenobarbital." IARC (2016) classified primidone as Group 2B, possibly carcinogenic to humans based on sufficient evidence of carcinogenicity in animals.	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA98, 100, 1535, 1537 w/ and w/o metabolic activation. Negative in *in vitro* mouse lymphoma cell assay (CCRIS, 2009d).]	Not applicable (mechanism for induction of tumors in mice thought to be non-genotoxic)	---	---
Salicylic acid	Negative in studies in mice and rats (SCCNFP, 2002).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* strains TA98, 100, 1535, 1537 w/ and w/o metabolic activation and in *E. coli* WP2 uvrA (CCRIS, 2010c)].	Not applicable (no increase in tumor incidence)	---	---
Sucralose	No increase in tumor incidence in 2-year oral dietary carcinogenicity studies in rats and mice at doses up to 1,500 mg/kg-d and 4,500 mg/kg-d, respectively (Mann et al., 2000a, b). Increase in hematopoietic neoplasias in male mice administered sucralose in feed at 2,000 ppm and 16,000 ppm through lifespan from gestation (but not in animals receiving 500 ppm or 8,000 ppm) (Soffritti et al., 2016).	Negative [Negative *in vitro* in bacterial reverse mutagenicity assay in *S. typhimurium* w/ and w/o metabolic activation. Negative *in vitro* in gene mutation assay in mouse lymphoma cells w/ and w/o metabolic activation, DNA repair assay in *E. coli* w/ and w/o metabolic activation, and DNA repair assay in rat hepatocytes. Positive in *in vitro* and *in vivo* Comet assays w/o activation. Negative in *in vivo* rat bone marrow chromosomal aberration assay, mouse micronucleus assay, and human lymphocyte chromosomal aberration assay (Berry et al., 2016).]	Not applicable (mechanism for development of tumors in one study in mice assumed to be nongenotoxic based on lack of evidence of genotoxicity).	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
Sulfadiazine	No evidence of carcinogenicity (RxList.com, 2019b).	No data	Not applicable (no increase in tumor incidence)	---	---
Sulfadimethoxine	No data	No data	Not applicable (no data)	---	---
Sulfamethoxazole	Increase in follicular cell adenomas or carcinomas of the thyroid in rats exposed at concentrations up to 600 mg/kg-d in the diet for 60 weeks (IARC, 2001; CCRIS, 2006f). Produced thyroid enlargement and hyperplasia in rats but not monkeys (IARC, 2001). Classified by IARC (2001) as Group 3: Not classifiable as to its carcinogenicity in humans, based on inadequate evidence in humans and limited evidence in experimental animals.	Mixed [Positive for *in vitro* bacterial reverse mutagenicity in *S. typhimurium* TA98 and 100 w/o activation but not in other Ames assays (CCRIS, 2006f). No increase in chromosomal aberrations in human lymphocytes *in vitro* (IARC, 2001).]	Not applicable (mechanism for development of cancers in rodents not likely to be relevant to humans, but some evidence of genotoxicity) **Use VSD approach to calculate comparison level (see Table 4-5)**	---	---
Testosterone	Cervical-uterine tumors and hepatomas in rodents, but only studies delivered it in subcutaneous implants (Drugs.com, 2019f; HSDB, 2017d).	Positive [Positive in *in vitro* micronucleus assay in mouse L929 cells (HSDB, 2017d).]	Not applicable (no relevant data located) **Use VSD approach to calculate comparison level (see Table 4-5)**	---	---
Theobromine	Long-term animal studies have not been conducted.	Mixed [Negative in *in vitro* bacterial reverse mutagenicity assays in *S. typhimurium*, strains TA97A, 98, 100, 102, 104, 1535, 1537, 1538 w/ and w/o metabolic activation but positive in *E. coli*. Positive in *in vitro* mouse lymphoma cell assay w/ and w/o activation. Mixed results for increases in SCEs in human lymphocyte cells *in vitro* (CCRIS, 2001c).]	Not applicable (no data)	---	---
Theophylline	No evidence of carcinogenicity in 2-year oral carcinogenicity studies in rats and mice	Negative [Negative in *in vitro* bacterial reverse mutagenicity assays in *S.*	Not applicable (no increase in tumor	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
	(CPDB, 2007a).	*typhimurium*, strains TA97, 98, 100, 102, 104, 1535, 1537, 1538 w/ and w/o metabolic activation (CCRIS, 2003). Negative in vitro in micronucleus and CHO tests systems (HSDB, 2016).].	incidence)		
Thiabendazole	No evidence of carcinogenicity in dietary studies in rats or mice, with administration from 65 weeks to 2 years (Fujii et al., 1991). U.S. EPA (2002) has classified thiabendazole as likely to be carcinogenic at doses high enough to cause disturbance of the thyroid hormone balance, but not likely to be carcinogenic at doses lower than those which could cause a disturbance of this hormonal balance.	Positive [Positive in *in vitro* bacterial reverse mutagenicity assay in *S. typhimurium*, strains TA97, 98, 100, 104 w/o metabolic activation, but negative in other assays w/ 98 and 100 w/ and w/o metabolic activation. Positive in *E. coli* strain WP2S. Positive in *in vitro* micronucleus assays in V79 and human lymphoblast cells (CCRIS, 2006g).]	Not applicable (no increase in tumor incidence in animal studies but U.S. EPA suggests can be carcinogenic at high doses) **Use VSD approach to calculate comparison level (see Table 4-5)**	---	---
Triclosan	No evidence of carcinogenicity in a 2-year oral dietary study in rats or in a 90-95 week oral dietary study in hamsters (NICNAS, 2009). Classified as Not likely to be carcinogenic to humans by U.S. EPA (1998). Increase in combined incidence of hepatocellular adenomas and carcinomas in 30 mg/kg-day dose group but not 10, 100, or 200 mg/kg-d groups, judged to be due to peroxisome proliferation and not relevant to carcinogenicity in humans (ITER, 2019).	Negative [Negative in multiple *in vitro* bacterial reverse mutagenicity assays in *S. typhimurium*, including strains TA92, 98, 100, 1535, 1537, 1538 w/ and w/o metabolic activation, and in CHO cells w/ and w/o metabolic activation (NICNAS, 2009). Mixed results in two *in vitro* chromosomal aberration assays in CHO cells. Negative results *in vitro* in multiple assays in mouse lymphoma cells w/ and w/o activation at concentrations that weren't cytotoxic, and in two UDS assays in rat hepatocytes. *In vivo*, no increase in chromosomal aberrations in rat or guinea pig bone marrow assays or in micronucleus assays in mice and guinea pigs (NICNAS, 2009).]	Not applicable (mechanism for development of cancers in rodents not likely to be relevant to humans)	---	---
Trimethoprim	No data	Positive [Positive in *in vitro* bacterial reverse mutagenicity assays in *S. typhimurium*, including strains TA98 and 1538 w/ and w/o metabolic activation, negative in TA97A,	Not applicable (No data)	---	---

Compound	Evidence	Genotoxicity assumption	Availability of tumor incidence data	Cancer SF (mg/kg-d)$^{-1}$	Comparison level based on CSF (µg/kg-d)*
		100, 102 and in *E. coli* WP2 uvrA w/ and w/o activation (CCRIS, 2004)].			

*Calculated assuming an acceptable lifetime excess cancer risk of 1 in one million and that a person is exposed to the chemical at this dose daily for a lifetime, or comparison level = 10^{-6} / (SF × 1000 µg/mg).

CCRIS – Chemical Carcinogenesis Research Information System; CHL – Chinese hamster lung; CHO – Chinese hamster ovary; CSF – cancer slope factor; F – female; HGPRT – Hypoxanthine-guanine phosphoribosyltransferase; IARC – International Agency for Research on Cancer; M – male; NLM – National Library of Medicine; NTP – National Toxicology Program; SCE – sister chromatid exchange; SF – slope factor; UDS – unscheduled DNA synthesis; VSD – Virtually Safe Dose

Table B-5. Comparison Levels for Compounds with Evidence of Genotoxic Carcinogenicity but No Tumor Incidence Data, Based on the Virtually Safe Dose (VSD) Method

Compound	Evidence	Genotoxicity assumption (see Table B-4)	Maximum tolerated dose (mg/kg-d)	Source	Comparison level based on VSD (µg/kg-d)*
Chloramphenicol	Induces aplastic anemia in humans, and this condition is related to the occurrence of leukemia; probably carcinogenic to humans (Group 2A) (IARC, 1990). Inadequate testing in animals.	Positive	300 (dog)†	HSDB, 2018	0.40
Pentoxifylline	Statistically significant increase in benign mammary fibroadenomas in female rats (Drugs.com, 2019e).	Positive	450 (mouse) 450 (rat)	Drugs.com, 2019e	0.60
Sulfamethoxazole	Increase in follicular cell adenomas or carcinomas of the thyroid in rats exposed at concentrations up to 600 mg/kg-d in the diet for 60 weeks (IARC, 2001; CCRIS, 2006f). Produced thyroid enlargement and hyperplasia in rats but not monkeys (IARC, 2001). Classified by IARC (2001) as Group 3: Not classifiable as to its carcinogenicity in humans, based on inadequate evidence in humans and limited evidence in experimental animals.	Mixed	Not available	Not available	Not available
Testosterone	Cervical-uterine tumors and hepatomas in rodents, but only studies delivered it in subcutaneous implants (Drugs.com, 2019f; HSDB, 2017d).	Mixed	Not available	Not available	Not available
Thiabendazole	No evidence of carcinogenicity in dietary studies in rats or mice, with administration from 65 weeks to 2 years (Fujii et al., 1991). U.S. EPA (2002) has classified thiabendazole as likely to be carcinogenic at doses high enough to cause disturbance of the thyroid hormone balance, but not likely to be carcinogenic at doses lower than those which could cause a disturbance of this hormonal balance.	Positive	100 (rat)‡	Roberts, No date	0.13

*Comparison level (µg/kg-d) = MTD (mg/kg-d) × 1,000 µg/mg/ 740,000

†No data available for rodents. MTD = 150 mg/kg-d in dog via intravenous administration; given that chloramphenicol is "readily absorbed from the gastrointestinal tract" (Kelly et al., 1951), a 50% oral absorption rate was conservatively assumed to convert to an oral MTD.

‡Per Roberts (No Date), severe effects on weight gain in a two-year oral study in rats "at doses above 200 mg/kg-d…suggests the maximum tolerated dose was exceeded." Based on this, the MTD was assumed to be 100 mg/kg-d.

IARC –International Agency for Research on Cancer; MTD – maximum tolerated dose; VSD – Virtually Safe Dose

Table B-6. Minimum Inhibitory Concentrations (MICs) for Antibiotics and Corresponding Comparison Levels

Antibiotic	MIC_{50}* (mg/g)	Comparison level (µg/kg-d) †
Amoxicillin	0.125 (*Clostridium* spp.; *Peptostreptococcus* spp.)	68
Azithromycin	0.06 (*Bacteroides capillosus* and *ureolyticus, Eubacterium* spp.)	33
Carbadox	NA	NA
Chloramphenicol	0.12 (*Fusobacterium* spp.)	66
Erythromycin	0.03 (*Bacteroides capillosus*; *Bifidobacterium* spp.; *Eubacterium* spp., *Lactobacillus* spp.)	16
Flumequine	0.25 (*E. coli*)	130
Lidocaine	Not available	Not available
Lincomycin	2 (*Lactobacillus* spp.)	1,100
Oxolinic acid	0.06 (*E. coli*)	33
Sulfadiazine	0.06 (*E. coli*) (with Trimethoprim)	33
Sulfadimethoxine	128 (*E. coli*)	70,400
Sulfamethoxazole	76 (*E. coli*)	41,800
Triclosan	5 (*E. coli*)†	2,750
Trimethoprim	0.05 (*E. coli*)	27

*Data obtained from KnowledgeBase (2020) Antimicrobial Index unless otherwise indicated
† Comparison level = MIC_{50} (mg/g) × MCC (220 g/d) × 1,000 (ug/g)/(FA (0.5) × SaF (10) × BW (80 kg))
‡ Source: Aiello et al. (2004)
BW − body weight; FA − fraction available; MCC − mass of colonic contents; MIC_{50} − minimum inhibitory concentration of 50% of strains of the most sensitive relevant organism representing human intestinal flora (*Escherichia coli*, and species of *Bacteroides, Bifidobacterium, Clostridium, Enterococcus, Eubacterium (Collinsella), Fusobacterium, Lactobacillus, Peptostreptococcus/Peptococcus*; Silley, 2007); SaF − safety factor

Table B-7. Comparison Level-Based DWELs for COIs Derived Using the Decision Tree Approach

	Comparison Level-Based DWELs (µg/L)								
Chemical	**U.S. EPA MCL, WA WQS, or WA MTCA GWC**	**Lowest of other existing ADI-based values**	**Noncancer toxicity data-based**	**Therapeutic dose-based**	**CSF from tumor data-based**	**VSD for carcinogens-based**	**MIC-based**	**DWEL (ng/L)**	**Basis of Value**
1,4-Dioxane	0.44 (WA DEQ, 2020)	0.37 (Cancer SF; OEHHA, 2020a)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	370	Existing value (Cancer SF; OEHHA, 2020a)
1,7-Dimethylxanthine	*no values*	*no values*	8.3 (Nawrot et al., 2003)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	8,300	NOAEL/LOAEL (Nawrot et al., 2003)
2,4-D	70 (U.S. EPA MCL)	30 (chronic HRL; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	30,000	Existing value (Chronic HRL; MDH, 2020)
4-Nonylphenol	*no values*	20 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	20,000	Existing value (HBV; MDH, 2020)
4-para-Nonylphenol	*no values*	20 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	20,000	Existing value (HBV; MDH, 2020)
4-tert-octylphenol	*no values*	100 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	100,000	Existing value (HBV; MDH, 2020)
Acesulfame-K	*no values*	150,000 (JECFA ADI; WHO, 1990)	120 (Bian et al., 2017)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	120,000	NOAEL/LOAEL (Bian et al., 2017)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
Acetaminophen	*no values*	*no values*	1,400 (Toyoda et al., 2018)	2.7 (RxList, 2019e)	5.0 (Flaks et al., 1985)	*not applicable*	*not applicable*	2,700	Therapeutic dose (RxList, 2019e)
Albuterol	*no values*	*no values*	2.5 (Drugs.com, 2019b)	0.0075 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	7.5	Therapeutic dose (RxList, 2019e)
Amoxicillin	*no values*	*no values*	5,000 (Drugs.com, 2019d)	31 (RxList, 2019e)	*not applicable*	*not applicable*	680 (Know-ledgeBase, 2020)	31,000	Therapeutic dose (RxList, 2019e)
Atenolol	*no values*	*no values*	2.6 (Bayliss et al., 2002; Lip et al., 1997; Lydakis et al., 1999)	1.0 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1,000	Therapeutic dose (RxList, 2019e)
Azithromycin	*no values*	*no values*	33 (Pfizer, 2016)	25 (RxList, 2019e)	*not applicable*	*not applicable*	330 (Know-ledgeBase, 2020)	25,000	Therapeutic dose (RxList, 2019e)
BPA (Bisphenol A)	800 (WA MTCA GWC Method B; WA DEQ, 2020)	20 (nHRL-chronic; MDH, 2015)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	20,000	Existing value (nHRL-chronic; MDH, 2015)
Bromacil	*no values*	80 (HA; U.S. EPA, 1987a)	13 (U.S. EPA, 1996)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	13,000	NOAEL/ LOAEL (U.S. EPA, 1996)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
Butalbital	*no values*	*no values*	*no data*	2.0 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	2,000	Therapeutic dose (RxList, 2019e)
Caffeine	*no values*	20,000 (CERHR ADI; NTP, 2008; Morgan et al., 2013)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	20,000,000	Existing value (CERHR; NTP 2008; Morgan et al., 2013)
Carbadox	*no values*	*no values*	33 (Yoshimura, 2002)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	33,000	NOAEL/LOAEL (Yoshimura, 2002)
Carbamazepine	*no values*	40 (chronic HBV; MDH, 2013b)	1 (Hernandez-Diaz et al., 2000; Samren et al., 1997; Samren et al., 1999)	0.33 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	330	Therapeutic dose (RxList, 2019e)
Carisoprodol	*no values*	*no values*	1,000 (NTP, 2000b)	10 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	10,000	Therapeutic dose (RxList, 2019e)
Chloramphenicol	*no values*	*no values*	8.3 (IARC, 1980)	0.0041 (RxList, 2019e)	*data not available*	4.0 (HSDB, 2018)	660 (Know-ledgeBase, 2020)	4.1	Therapeutic dose (RxList, 2019e)
Chloridazon	*no values*	1,000 (ADI; EFSA, 2007)	180 (U.S. EPA, 2005a)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	180,000	NOAEL/LOAEL (U.S. EPA, 2005a)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
Clofibric Acid	*no values*	*no values*	66 (IARC, 1980)	8.3 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	8,300	Therapeutic dose (RxList, 2019e)
Cotinine	*no values*	*no values*	0.8 (HSDB, 2009a)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	800	NOAEL/LOAEL (HSDB, 2009a)
Cyanazine	*no values*	*no values*	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	1,000	Existing value (HBV; MDH, 2020)
Diaminochlorotriazine (DACT)	3 (MCL; U.S. EPA, 2020)	38 (MADL; OEHHA, 2016)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	3,000	Existing value (MCL; U.S. EPA, 2020)
Desethylatrazine (DEA)	3 (MCL; U.S. EPA, 2020)	38 (MADL; OEHHA, 2016)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	3,000	Existing value (MCL; U.S. EPA, 2020)
N,N-Diethyl-meta-toluamide (DEET)	*no values*	200 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	200,000	Existing value (HBV; MDH, 2020)
Dehydronifedipine	*no values*	*no values*	20 (HSDB, 2010)	1.2 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1,200	Therapeutic dose (RxList, 2019e)
Diazepam	*no values*	*no values*	800 (Drugs.com, 2019g)	0.083 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	83	Therapeutic dose (RxList, 2019e)
Diclofenac	*no values*	*no values*	0.83 (Vyas et al., 2018)	4.1 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	830	NOAEL/LOAEL (Vyas et al., 2018)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
				Comparison Level-Based DWELs (µg/L)					
Dilantin	*no values*	*no values*	1.4 (Hernandez-Diaz et al., 2000)	1.2 (RxList, 2019e)	8.3 (NTP, 1993)	*not applicable*	*not applicable*	1,200	Therapeutic dose (RxList, 2019e)
Diltiazem	*no values*	*no values*	25 (Drugs.com, 2019b)	5.0 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	5,000	Therapeutic dose (RxList, 2019e)
Diuron	32 (WA MTCA GWC Method B; WA DEQ, 2020)	20 (RfD; U.S. EPA, 1988b)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	20,000	Existing value (RfD; U.S. EPA, 1988b)
Erythromycin	*no values*	*no values*	1,200 (Drugs.com, 2018a)	100 (RxList, 2019e)	*not applicable*	*not applicable*	160 (Know-ledgeBase, 2020)	100,000	Therapeutic dose (RxList, 2019e)
Estradiol	*no values*	0.00026 (California SF; OEHHA, 2020c)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	0.26	Existing value (California SF; OEHHA, 2020c)
Estrone	*no values*	*no values*	0.0040 (Mashchak et al.,1982)	0.000058 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	0.058	Therapeutic dose (RxList, 2019e)
Ethinyl Estradiol - 17 alpha	*no values*	0.0002 (chronic HBV; MDH, 2020)	0.016 (Kirigaya et al., 2006)	0.000083 (RxList, 2019e)	0.052 (CPDB, 2007f)	*not applicable*	*not applicable*	0.083	Therapeutic dose (RxList, 2019e)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
				Comparison Level-Based DWELs (µg/L)					
Flumequine	*no values*	*no values*	25 (EMEA, 1999)	*no values*	*not applicable*	*not applicable*	1,300 (Know-ledgeBase, 2020)	25,000	NOAEL/LOAEL (EMEA, 1999)
Fluoxetine	*no values*	*no values*	0.96 (NTP, 2004)	1.1 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	960	NOAEL/LOAEL (NTP, 2004)
Gemfibrozil	*no values*	*no values*	30 (Fitzgerald et al., 1981)	5.0 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	5,000	Therapeutic dose (RxList, 2019e)
Ibuprofen	*no values*	*no values*	10 (Momma and Takeuchi, 1983)	8.3 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	8,300	Therapeutic dose (RxList, 2019e)
Iohexol	*no values*	*no values*	500 (Parravicini et al., 1996)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	500,000	NOAEL/LOAEL (Parravicini et al., 1996)
Iopromide	*no values*	*no values*	500 (Parravicini et al., 1996)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	500,000	NOAEL/LOAEL (Parravicini et al., 1996)
Ketorolac	*no values*	*no values*	90 (FDA, 2009)	1.6 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1,600	Therapeutic dose (RxList, 2019e)
Lidocaine	*no values*	*no values*	19 (Morishima et al., 1990)	10 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	10,000	Therapeutic dose (RxList, 2019e)
Lincomycin	*no values*	300 (JECFA ADI; WHO, 2004)	500 (Pharmacia & Upjohn, 1995)	33 (RxList, 2019e)	*not applicable*	*not applicable*	11,000 (Know-ledgeBase, 2020)	33,000	Therapeutic dose (RxList, 2019e)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
			Comparison Level-Based DWELs (µg/L)						
Linuron	32 (WA MTCA GWC Method B; WA DEQ, 2020)	1 (HRL; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	1,000	Existing value (HRL; MDH, 2020)
Lopressor	*no values*	*no values*	11 (el-Sayed et al., 1998)	1.0 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1,000	Therapeutic dose (RxList, 2019e)
Meclofenamic Acid	*no values*	*no values*	30 (Petrere et al., 1985)	83 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	30,000	NOAEL/LOAEL (Petrere et al., 1985)
Meprobamate	*no values*	*no values*	100 (Caldwell and Spille, 1964)	22 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	22,000	Therapeutic dose (RxList, 2019e)
Metformin	*no values*	*no values*	2,000 (Quaile et al., 2010)	41 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	41,000	Therapeutic dose (RxList, 2019e)
Methylparaben	*no values*	100,000 (JECFA ADI; WHO, 2006)	5,500 (Food Drug and Research Labs, Inc., 1972 as cited in U.S. EPA, 2005b)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	5,500,000	NOAEL/LOAEL (Food Drug and Research Labs, Inc., 1972 as cited in U.S. EPA, 2005b)
Naproxen	*no values*	*no values*	200 (Roche, 2012)	13 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	13,000	Therapeutic dose (RxList, 2019e)
Nifedipine	*no values*	*no values*	20 (HSDB, 2010)	1.2 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1,200	Therapeutic dose (RxList, 2019e)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
N-Nitroso dimethylamine (NDMA)	0.00086 (WA MTCA GWC Method B; WA DEQ, 2020)	0.005 (HBV; MDH; 2019)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	0.86	Existing value (WA MTCA GW Cleanup level Method B; WA DEQ, 2020)
Norethisterone	*no values*	*no values*	3.3 (IARC, 1979)	0.0014 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	1.4	Therapeutic dose (RxList, 2019e)
OUST (Sulfometuron methyl)	*no values*	2,750 (RfD; U.S. EPA, 2008)	300 (Hazelton Laboratories America, Inc., 1990 as cited in CalEPA, 2002)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	300,000	NOAEL/LOAEL (Hazelton Laboratories America, Inc., 1990 as cited in CalEPA, 2002)
Oxolinic acid	*no values*	*no values*	110 (Yamada et al., 1994)	*no values*	*not applicable*	*not applicable*	330 (Know-ledgeBase, 2020)	110,000	NOAEL/LOAEL (Yamada et al., 1994)
Pentoxifylline	*no values*	*no values*	50 (Shepard and Lermire, 2004)	3.3 (RxList, 2019e)	*not applicable*	6.0 (Drugs.com, 2019e)	*not applicable*	3,300	Therapeutic dose (RxList, 2019e)
Primidone	*no values*	*no values*	40 (Pizzi et al.,1996)	0.41 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	410	Therapeutic dose (RxList, 2019e)

Chemical	Comparison Level-Based DWELs (µg/L)								
	U.S. EPA MCL, WA WQS, or WA MTCA GWC	**Lowest of other existing ADI-based values**	**Noncancer toxicity data-based**	**Therapeutic dose-based**	**CSF from tumor data-based**	**VSD for carcinogens-based**	**MIC-based**	**DWEL (ng/L)**	**Basis of Value**
Quinoline	0.015 (WA MTCA GWC Method B; WA DEQ, 2020)	0.0033 (SF, U.S. EPA, 2001)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	3.3	Existing value (SF; U.S. EPA, 2001)
Salicylic Acid	*no values*	*no values*	66 (HSDB, 2009b)	13 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	13,000	Therapeutic dose (RxList, 2019e)
Simazine	0.73 (WA MTCA GWC Method B; WA DEQ, 2020)	4 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	730	Existing value (WA MTCA GW cleanup level Method B; WA DEQ, 2020)
Sucralose	*no values*	150,000 (JECFA ADI; EC, 2000)	1,500 (Berry et al., 2016)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	1,500,000	NOAEL/LOAEL (Berry et al., 2016)
Sulfadiazine	*no values*	*no values*	120 (Panciera and Post, 1992)	41 (RxList, 2019e)	*not applicable*	*not applicable*	330 (Know-ledgeBase, 2020)	41,000	Therapeutic dose (RxList, 2019e)
Sulfadimethoxine	*no values*	*no values*	1,600 (Zoetis, 2016)	*no values*	*not applicable*	*not applicable*	700,000 (Know-ledgeBase, 2020)	1,600,000	NOAEL/LOAEL (Zoetis, 2016)
Sulfamethoxazole	*no values*	100 (HBV; MDH, 2013a)	510 (Monarch Pharmaceuti cals, No date)	5.3 (RxList, 2019e)	*not applicable*	*data not available*	410,000 (Know-ledgeBase, 2020)	5,300	Therapeutic dose (RxList, 2019e)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
Testosterone	*no values*	*no values*	1.3 (IARC, 1979)	0.20 (RxList, 2019e)	*not applicable*	*data not available*	*not applicable*	200	Therapeutic dose (RxList, 2019e)
Theobromine	*no values*	*no values*	6.6 (Chorostowska-Wynimko et al., 2004)	*not applicable*	*not applicable*	*not applicable*	*not applicable*	6,600	NOAEL/LOAEL (Chorostowska-Wynimko et al., 2004)
Theophylline	*no values*	*no values*	400 (Drugs.com, 2018c)	0.66 (RxList, 2019e)	*not applicable*	*not applicable*	*not applicable*	660	Therapeutic dose (RxList, 2019e)
Thiabendazole	*no values*	1,000 (RfD; U.S. EPA, 2002)	250 (Lankas et al., 2001)	*not applicable*	*not applicable*	1.3 (Roberts, No date)	*not applicable*	1,300	VSD (Roberts, No date)
Triclosan	*no values*	50 (HBV; MDH, 2020)	2.3 (Louis et al., 2017)	*not applicable*	*not applicable*	*not applicable*	27,000 (Know-ledgeBase, 2020)	2,300	NOAEL/LOAEL (Louis et al., 2017)
Trimethoprim	*no values*	*no values*	14 (Pfizer, 2018)	2.6 (RxList, 2019e)	*not applicable*	*not applicable*	270 (Know-ledgeBase, 2020)	2,600	Therapeutic dose (RxList, 2019e)
Tris(2-carboxyethyl)-phosphine (TCEP)	*no values*	0.50 (SF; U.S. EPA, 2009)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	500	Existing value (SF; U.S. EPA, 2009)
Tris(1-chloro-2-propyl) phosphate (TCPP)	*no values*	200 (RfD; U.S. EPA, 2012c)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	200,000	Existing value (RfD; U.S. EPA, 2012c)
Tris(1,3-dichloroisopropyl)-phosphate (TDCPP)	*no values*	2.0 (NSRL; OEHHA, 2012)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	2,000	Existing value (NSRL; OEHHA, 2012)

Comparison Level-Based DWELs (µg/L)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
Perfluoro butanoic acid-PFBA	*no values*	7.0 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	7,000	Existing value (HBV; MDH, 2020)
Perfluoro octanesulfonate-PFOS	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	0.015 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	15	Existing value (HBV; MDH, 2020)
Perfluoro octanesulfonic acid	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	0.03 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	30	Existing value (HBV; MDH, 2020)
Perfluoro octanoic acid - PFOA	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	0.035 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	35	Existing value (HBV; MDH, 2020)
Perfluoro-1-butanesulfonate	*no values*	2 (HBV; MDH, 2020)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	2,000	Existing value (HBV; MDH, 2020)
Perfluoro-1-butanesulfonic acid	*no values*	200 (RfD; U.S. EPA, 2014)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	200,000	Existing value (RfD; U.S. EPA, 2014)
Perfluoro-n-heptanoic acid	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	*no values*	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	70	Existing value (HA for PFOA + PFOS; U.S. EPA, 2016)
Perfluoro-n-hexanoic acid	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	*no values*	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	70	Existing value (HA for PFOA + PFOS; U.S. EPA, 2016)

Chemical	U.S. EPA MCL, WA WQS, or WA MTCA GWC	Lowest of other existing ADI-based values	Noncancer toxicity data-based	Therapeutic dose-based	CSF from tumor data-based	VSD for carcinogens-based	MIC-based	DWEL (ng/L)	Basis of Value
			Comparison Level-Based DWELs (µg/L)						
Perfluoro-n-nonanoic acid	*no values*	0.030 (MRL; ATSDR, 2018)	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	30	Existing value (MRL; ATSDR, 2018)
Perfluoropentanoic acid	0.07 (HA for PFOA + PFOS; U.S. EPA, 2016)	*no values*	*not determined*	*not applicable*	*not determined*	*not determined*	*not applicable*	70	Existing value (HA for PFOA + PFOS; U.S. EPA, 2016)

REFERENCES

Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, Mills RF, Nicholson JS, and Williams GA. 1970. Some aspects of the pharmacology, metabolism, and toxicology of ibuprofen. *Rheumatol Phys Med*. 11(Suppl.):9-22.

Aiello AE, Marshall B, Levy SB, Della-Latta P, and Larson E. 2004. Relationship between triclosan and susceptibilities of bacteria isolated from hands in the community. *Antimicrob Agents Chemother*. 48(8):2973-9.

ATSDR. 2012a. *Toxicological Profile for 1,4-Dioxane*. Agency for Toxic Substances and Disease Registry. Centers for Disease Control. Atlanta, GA. Accessed May 28, 2020 at https://www.atsdr.cdc.gov/toxprofiles/tp187.pdf.

ATSDR. 2012b. *Toxicological Profile for Phosphate Ester Flame Retardants*. Agency for Toxic Substances and Disease Registry. Centers for Disease Control. Atlanta, GA. Accessed May 28, 2020 at https://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf.

ATSDR. 2017a. *Toxicological Profile for 2,4-Dichlorophenoxyacetic Acid (2,4-D)*. Agency for Toxic Substances and Disease Registry. Centers for Disease Control. Atlanta, GA. Accessed May 28, 2020 at https://www.atsdr.cdc.gov/toxprofiles/tp210.pdf.

ATSDR. 2017b. *Toxicological Profile for DEET (N,N-Diethyl-meta-toluamide).* Agency for Toxic Substances and Disease Registry. Centers for Disease Control. Atlanta, GA. Accessed May 28, 2020 at https://www.atsdr.cdc.gov/toxprofiles/tp185.pdf.

ATSDR. 2018. *Toxicological Profile for Perfluoroalkyls*. Agency for Toxic Substances and Disease Registry. Centers for Disease Control. Atlanta, GA. Accessed May 28, 2020 at https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

Bayliss H, Churchill D, Beevers M, and Beevers DG. 2002. Anti-hypertensive drugs in pregnancy and fetal growth: evidence for "pharmacological programming" in the first trimester? *Hypertens Pregnancy*. 21(2):161-174.

Bendele, RA, Adams ER, Hoffman WP, Gries CL, and Morton DM. 1992. Carcinogenicity studies of fluoxetine hydrochloride in rats and mice. *Cancer Res*., 52(24):6931-6935.

Berger FM, Kletzkin M, Ludwig BJ, Margolin S, and Powell LS. 1959. Unusual muscle relaxant and analgesic properties of n-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (Carisoprodol). *J Pharmacol Exp Ther*. 127:66-74.

Berry C, Brusick D, Cohen SM, Hardisty JF, Grotz VL, and Williams GM. 2016. Sucralose non-carcinogenicity: A review of the scientific and regulatory rationale. *Nutr Cancer*. 68(8):1247-1261.

Bian X, Chi L, Gao B, Tu P, Ru H, and Lu K. 2017. The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. *PLoS One*. Jun 8;12(6):e0178426.

Caldwell MB and Spille DF. 1964. Effect on rat progeny of daily administration of meprobamate during pregnancy and lactation. *Nature*. 202:832-3.

CalEPA. 1997. Summary of Toxicology Data: Bromacil. California Environmental Protection Agency, Department of Pesticide Regulation. November 14.

CalEPA. 2000. Summary of Toxicology Data: Pyrazon. California Environmental Protection Agency, Department of Pesticide Regulation. May 17.

CalEPA. 2002. Summary of Toxicology Data: Sulfometuron Methyl. California Environmental Protection Agency, Department of Pesticide Regulation. November 12.

CalEPA. 2018. NDMA and Other Nitrosamines - Drinking Water Issues. California Environmental Protection Agency, State Water Resources Control Board. August 23. Accessed May 28, 2020 at https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/NDMA.html

CalEPA. 2019. 1,4-Dioxane. California Environmental Protection Agency, State Water Resources Control Board. June 26. Accessed May 28, 2020 at https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/14-Dioxane.html

CCRIS. 1992a. Chloramphenicol. CASRN 56-75-7. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 1992b. Methyl-p-hydroxybenzoate. CASRN 99-76-3. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 1993. Carisoprodol. CASRN 78-44-4. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 1994. Nifedipine. CASRN 21829-25-4. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 1995. Azithromycin. CASRN: 83905-01-5. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 1997. (S)-(-)-Cotinine. CASRN 486-56-6. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2000. Ibuprofen. CASRN 15687-27-1. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2001a. Naproxen. CASRN 22204-53-1. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2001b. Oxolinic Acid. CASRN 14698-29-4. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2001c. Theobromine. CASRN 83-67-0. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2003. Theophylline. CASRN 58-55-9. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2004. Trimethoprim. CASRN 738-70-5. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2005. Pentoxifylline. CASRN 6493-05-6. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006a. Atenolol. CASRN: 29122-68-7. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006b. Diazepam. CASRN 439-14-5. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006c. Erythromycin. CASRN 114-07-8. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006d. Metoprolol. CASRN 37350-58-6. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006e. Norethindrone. CASRN 68-22-4. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006f. Sulfamethoxazole. CASRN 723-46-6. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2006g. Thiabendazole. CASRN 148-79-8. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2007. Bromacil. CASRN 314-40-9. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2008. Phenytoin. CASRN 57-41-0. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2009a. Acesulfame K. CASRN 55589-62-3. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2009b. Clofibrate. CASRN 637-07-0. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2009c. Metformin. CASRN 657-24-9. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2009d. Primidone. CASRN 125-33-7. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2010a. Acetaminophen. CASRN 103-90-2. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2010b. Caffeine (CAS 58-08-2). Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2010c. Salicyclic Acid. CASRN 69-72-7. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

CCRIS. 2011. Ethinylestradiol. CASRN 57-63-6. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. Accessed May 28, 2020 at https://www.nlm.nih.gov/toxnet/index.html

Chorostowska-Wynimko J, Skopińska-Rózewska E, Sommer E, Rogala E, Skopiński P, and Wojtasik E. 2004. Multiple effects of theobromine on fetus development and postnatal status of the immune system. *Int J Tissue React*. 26(1-2):53-60.

CPDB. 2007a. Listing for Theophylline. CASRN 58-55-9. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2007b. Caffeine. CASRN 58-08-2. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2007c. Acesulfame-K. CASRN 55589-62-3. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2007d. Diazepam. CASRN 439-14-5. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2007e. Primidone. CASRN 125-33-7. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2007f. Listing for Ethinyl Estradiol. CASRN 57-63-6. Cancer Potency Database University of California, Berkeley, CA, Accessed May 28, 2020 at https://www.toxinfo.io

CPDB. 2019. Acetaminophen. CASRN 103-90-2. Cancer Potency Database. University of California, Berkeley, CA. Accessed May 28, 2020 at https://www.toxinfo.io

Drugs.com. 2018a. Professional Listing for E.E.S., 400 Tablets (Erythromycin Ethylsuccinate) Tablet, Granule for Oral Suspension. Accessed August 5, 2019 at http://www.drugs.com/pro/e-e-s-400-tablets.html.

Drugs.com. 2018b. Professional Listing for Pentoxifylline, Tablet, Extended Release. Accessed August 5, 2019 at http://www.drugs.com/pro/pentoxifylline.html.

Drugs.com. 2018c. Professional Listing for Theophylline. Accessed August 5, 2019 at http://www.drugs.com/pro/theophylline.html.

Drugs.com. 2019a. Professional Listing for Meclofenamate Sodium. Drugsite Trust, Aukland, NZ. Accessed May 28, 2020 at https://www.rxlist.com/meclofenamate-drug.htm#description.

Drugs.com. 2019b. Professional Listing for Albuterol (Albuterol Sulfate) Tablets. Accessed May 28, 2020 at http://www.drugs.com/pro/albuterol.html.

Drugs.com. 2019c. Professional Listing for Dolgic Plus (Butalbital, Acetaminophen and Caffeine) Tablet. Accessed May 28, 2020 at http://www.drugs.com/pro/dolgic-plus.html.

Drugs.com. 2019d. Professional Listing for Amoxicillin, Capsule; Powder, for Oral Suspension; Tablet, Chewable. Accessed May 28, 2020 at http://www.drugs.com/pro/amoxicillin.html.

Drugs.com. 2019e. Professional Listing for Pentoxifylline, Tablet, Extended Release. Accessed May 28, 2020 at http://www.drugs.com/pro/pentoxifylline.html.

Drugs.com. 2019f. Professional Listing for AndroGel (testosterone). Accessed May 28, 2020 at from http://www.drugs.com/pro/androgel.html.

Drugs.com. 2019g. Professional Listing for Diazepam. Accessed May 28, 2020 at http://www.drugs.com/pro/diazepam-injection.html.

Drugs.com. 2019h. Professional Listing for Dilt-CD (diltiazem hydrochloride) capsule, extended release. Accessed May 28, 2020 at http://www.drugs.com/pro/dilt-cd.html.

DrugLib.com. 2017. Bactrim IV (Trimethoprim and Sulfamethoxazole) - Drug Interactions, Contraindications, Overdosage, etc. Accessed August 5, 2019 at http://www.druglib.com/druginfo/bactrim-iv/interactions_overdosage_contraindications/.

EC. 2000. Opinion of the Scientific Committee on Food on Sucralose. European Commission. Accessed May 28, 2020 at https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf.

EC. 2005. Extended Opinion on the Safety Evaluation of Parabens. Scientific Committee on Consumer Products (SCCP). European Commission. SCCP/0873/05. Accessed May 28, 2020 at https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_019.pdf.

EFSA. 2007. Conclusions regarding the peer review of the pesticide risk assessment of the active substance: Chloridazon. July 27. European Food Safety Authority. *EFSA Scientific Report*. 108:1-82. Accessed May 28, 2020 at https://www.efsa.europa.eu/en/efsajournal/pub/rn-108.

EFSA. 2015. Scientific opinion on the safety of caffeine. EFSA Panel on Dietetic Products, Nutrition and Allergies. European Food Safety Authority. Parma, Italy. *EFSA Journal*. 13(5): 4102. Accessed May 28, 2020 at https://www.efsa.europa.eu/en/efsajournal/pub/4102.

EFSA. 2017. Bisphenol A (BPA) hazard assessment protocol. Technical Report. European Food Safety Authority. November 30. Accessed May 28, 2020 at https://www.efsa.europa.eu/en/supporting/pub/en-1354

el-Sayed MG, el-Sayed MT, Elazab Abd el S, Hafeiz MH, el-Komy AA, and Hassan E. 1998. Effects of some beta-adrenergic blockers on male fertility parameters in rats. *Dtsch Tierarztl Wochenschr*. 105(1):10-2.

EMA. 2003. *Diclofenac: Summary Report*. Committee for Veterinary Medicinal Products. European Agency for the Evaluation of Medicinal Products. September. Accessed May 28, 2020 at https://www.ema.europa.eu/en/documents/mrl-report/diclofenac-summary-report-committee-veterinary-medicinal-products_en.pdf.

EMEA. 1999. *Committee for Veterinary Medicinal Products: Flumequine, Summary Report*. European Agency for the Evaluation of Medicinal Products. London, UK. Accessed May 28, 2020 at https://www.ema.europa.eu/en/documents/mrl-report/flumequine-summary-report-2-committee-veterinary-medicinal-products_en.pdf.

FDA. 2009. Approval for Acuvail. U.S. Food and Drug Administration, Drugs@FDA. Accessed May 28, 2020 at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022427s000_SumR.pdf.

FDA. 2014. Final Report for the Review of Literature and Data on BPA. U.S Food and Drug Administration. Accessed May 28, 2020 at https://www.fda.gov/media/90546/download

Fitzgerald JE, Sanyer JL, Schardein JL, Lake RS, McGuire EJ, and de la Iglesia FA. 1981. Carcinogen bioassay and mutagenicity studies with the hypolipidemic drug gemfibrozil. *J Natl Cancer Inst.* 67:1105–1116.

Flaks B, Flaks A, and Shaw AP. 1985. Induction by paracetamol of bladder and liver tumours in the rat. Effects on hepatocyte fine structure. *Acta Pathol Microbiol Immunol Scand A*. 93(6):367-77.

Fujii T, Mikuriya H, and Sasaki M. 1991. Chronic oral toxicity and carcinogenicity study of thiabendazole in rats. *Food Chem Toxicol*. 29(11):771-775.

Gonzalez FJ, Peters JM, and Cattley RC. 1998. Mechanism of action of the nongenotoxic peroxisome proliferators: role of the peroxisome proliferator-activator receptor alpha. *J Natl Cancer Inst*. 90(22):1702-9.

HCN. 2005. Nicotine (CASRN 54-11-5). Health-based Reassessment of Administrative Occupational Exposure Limit. Health Council of the Netherlands.

HDR. 2019. Tracer test and water quality monitoring (Task 2.1.3). LOTT Clean Water Alliance reclaimed water infiltration study. Report. HDR, Olympia, WA.

Hernández-Díaz S, Werler MM, Walker AM, and Mitchell AA. 2000. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 343(22):1608-14.

HSDB. 2003a. Atenolol. CASRN 29122-68-7. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+6526.

HSDB. 2003b. Diltiazem. CASRN 42399-41-7. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+6528.

HSDB. 2005a. Albuterol. CASRN 18559-94-9. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7206.

HSDB. 2005b. Fluoxetine hydrochloride. CAS RN 56296-78-7. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+6633.

HSDB. 2009a. Nicotine. CASRN 54-11-5. Hazardous Substances Data Bank. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1107.

HSDB. 2009b. Salicylic Acid. CASRN 69-72-7. Hazardous Substances Data Bank. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+672.

HSDB. 2010. Nifedipine. CASRN 21829-25-4. Hazardous Substances Data Bank. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7775.

HSDB. 2011. Diazepam. CASRN 439-14-5. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3057.

HSDB. 2013. Lincomycin. CAS 154-21-2. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3109.

HSDB. 2015. Lidocaine. CASRN 137-58-6. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3350.

HSDB. 2016. Theophylline. CASRN 58-55-9. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3399.

HSDB. 2017a. Amoxicillin. CASRN 26787-78-0. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3204.

HSDB. 2017b. Carbadox. CASRN 6804-07-5. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7028.

HSDB. 2017c. Flumequine. CASRN 42835-25-6. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7034.

HSDB. 2017d. Testosterone. CASRN 58-22-0. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3398.

HSDB. 2018. Chloramphenicol. CASRN 56-75-7. Hazardous Substances Data Bank. U.S. National Library of Medicine. Accessed May 28, 2020 at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+3027.

IARC. 1979. Sex Hormones (II). Volume 21. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono21.pdf.

IARC. 1980. Some Pharmaceutical Drugs. Volume 24. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono24.pdf.

IARC. 1987. Oestrogens, Progestins, and Combinations. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7: Overall Evaluation of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*. Pp. 272. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/Suppl7.pdf.

IARC. 1990. Pharmaceutical Drugs. Volume 50. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono50.pdf.

IARC. 1991. Caffeine. Volume 51. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono51.pdf.

IARC. 1996a. Clofibrate. Volume 66: Some Pharmaceutical Drugs. p. 391. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono66.pdf.

IARC. 1996b. Gemfibrozil. Volume 66: Some Pharmaceutical Drugs. *Monographs on the Evaluation of Carcinogenic Risks to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono66.pdf.

IARC. 1996c. Phenytoin. Volume 66: Some Pharmaceutical Drugs. p. 175. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono66.pdf.

IARC. 1999. Paracetamol. Volume 73: Some Chemicals That Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances p. 401. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono73.pdf

IARC. 2001. Sulfamethoxazole. Volume 79: Some Thyrotropic Agents. p. 361. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono79.pdf.

IARC. 2016. Primidone. In Volume 108: Some Drugs and Herbal Products. *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, World Health Organization, Geneva. Accessed May 28, 2020 at https://monographs.iarc.fr/wp-content/uploads/2018/06/mono108.pdf.

ITER. 2019. Triclosan. CASRN 3380-34-5. International Toxicity Estimates for Risk. National Library of Medicine. Accessed May 28, 2020 at http://www.iter.tera.org/

Jack D, Poynter D, and Spurling NW. 1983. Beta-adrenoceptor stimulants and mesovarian leiomyomas in the rat. *Toxicology*. 27(3-4):315-20.

Kadotani S, Arisawa M, and Maruyama HB. 1984. Mutagenicity examination of several non-steroidal anti-inflammatory drugs in bacterial systems. *Mutat Res*. 138(2-3):133-6.

Kelly RS, Hunt Jr AD, and Tashman SG. 1951. Studies on the absorption and distribution of chloramphenicol. *Pediatrics*. 8(3). Accessed May 28, 2020 at https://pediatrics.aappublications.org/content/8/3/362.

Kirigaya A, Hayashi S, Iguchi T, and Sato T. 2006. Developmental effects of ethinylestradiol on reproductive organs of female mice. *In Vivo*. 20(6B):867-73.

KnowledgeBase. 2020. Antimicrobial Index. Accessed May 28, 2020 at http://antibiotics.toku-e.com/.

Lankas GR, Nakatsuka T, Ban Y, Komatsu T, and Matsumoto H. 2001. Developmental toxicity of orally administered thiabendazole in ICR mice. *Food Chem Toxicol*. 39(4):367-74.

Lip GY, Beevers M, Churchill D, Shaffer LM, and Beevers DG. 1997. Effect of atenolol on birth weight. *Am J Cardiol* 79(10):1436-1438.

Louis GW, Hallinger DR, Braxton MJ, Kamel A, and Stoker TE. 2017. Effects of chronic exposure to triclosan on reproductive and thyroid endpoints in the adult Wistar female rat. *J Toxicol Environ Health A*. 80(4):236-249.

Lydakis C, Lip GY, Beevers M, and Beevers DG. 1999. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens*. 12(6):541-547.

Mann SW, Yuschak MM, Amyes SJ, Aughton P, and Finn JP. 2000a. A combined chronic toxicity/carcinogenicity study of sucralose in Sprague-Dawley rats. *Food Chem Toxicol*. 38 Suppl 2:S71-89.

Mann SW, Yuschak MM, Amyes SJ, Aughton P, and Finn JP. 2000b. A carcinogenicity study of sucralose in the CD-1 mouse. *Food Chem Toxicol*. 38 Suppl 2:S91-7.

Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF, and Mishell DR Jr. 1982. Comparison of pharmacodynamic properties of various estrogen formulations. *Am J Obstet Gynecol*. 144(5):511-518.

McEvoy GK. 2003. American Hospital Formulary Service—Drug Information 2003. American Society of Health-System Pharmacists, Inc., Bethesda, MD.

MDH. 2013a. 2013 Health Based Value for Groundwater: Sulfamethoxazole. CASRN 723-46-6. Minnesota Department of Health. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/sulfamethoxsum.pdf.

MDH. 2013b. Toxicological Summary for Carbamazepine. CASRN 298-46-4. Minnesota Department of Health. September 30. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/carbamazepine.pdf.

MDH. 2013c. Toxicological Summary for N, N-Diethyl-3-methylbenzamide (DEET). CASRN 134-62-3. Minnesota Department of Health. September. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/deet.pdf.

MDH. 2015. Toxicological Summary for Bisphenol A. CASRN 80-05-7. Minnesota Department of Health. August. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/bpatoxsumm.pdf

MDH. 2018. Toxicological Summary for Cyanazine. CASRN 21725-46-2. Minnesota Department of Health. August. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/cyanazine.pdf.

MDH. 2020. Human Health-Based Water Guidance Table. Minnesota Department of Health. Accessed May 28, 2020 at https://www.health.state.mn.us/communities/environment/risk/guidance/gw/table.html.

Micromedex Thomson Health Care. 2006. USPDI—Drug Information for the Health Care Professional, MICROMEDEX Thomson Health Care, Greenwood Village, CO.

Momma K and Takeuchi H. 1983. Constriction of fetal ductus arteriosus by non-steroidal anti-inflammatory drugs. *Prostaglandin*s. 26(4):631-643.

Monarch Pharmaceuticals. No date. Product label for Septra® tablets (trimethoprim and sulfamethoxazole). Accessed May 28, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017376s060lbl.pdf.

Morgan S, Koren G, and Bozzo P. 2013. Is caffeine consumption safe during pregnancy? *Can Fam Physician*. 59(4):361-362.

Morishima HO, Finster M, Arthur GR, and Covino BG. 1990. Pregnancy does not alter lidocaine toxicity. *Am J Obstet Gynecol*. 162(5):1320-1324.

Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, and Feeley M. 2003. Effects of caffeine on human health. *Food Addit Contam*. 20(1):1-30.

NICNAS. 2009. *Triclosan. Priority Existing Chemical Assessment Report No. 30*. National Industrial Chemicals Notification and Assessment Scheme. Sydney, Australia. January. Accessed May 28, 2020 at https://www.nicnas.gov.au/chemical-information/factsheets/chemical-name/triclosan.

NICNAS. 2016. *Urea, N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl)-: Human Health Tier II Assessment.* National Industrial Chemicals Notification and Assessment Scheme. Sydney, Australia. February 5. Accessed May 28, 2020 at https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1876#health.

Novartis. 2010. Product label for Tegretol (carbamazepine USP). Novartis Pharmaceuticals Corporation. U.S. FDA Center for Drug Evaluation and Research, Drugs@FDA. Accessed May 28, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016608s100s102,018281s049s050,018927s041s042,020234s031s033lbl.pdf.

NTP. 1993. *TR-404: Toxicology and Carcinogenesis Studies of 5,5- Diphenylhydantoin (CAS No. 57-41-0) (Phenytoin) in F344/N Rats and B6C3F1 Mice (Feed Studies).* National Toxicology Program. Research Triangle Park, NC. Accessed May 28, 2020 at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr404.pdf.

NTP. 2000a. *Estrogens (Not Conjugated). Ninth Report on Carcinogens.* National Toxicology Program. Research Triangle Park, NC.

NTP. 2000b. *Toxicity Studies of Carisoprodol (CAS No. 78-44-4) Administered by Gavage to F344/N Rats and B6C3F1 Mice*. NIH Number: 00-4404. National Toxicology Program, Research Triangle Park, NC. Accessed May 28, 2020 at https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox056.pdf.

NTP. 2000c. Ethinylestradiol. *Ninth Report on Carcinogens.* National Toxicology Program. Research Triangle Park, NC.

NTP. 2000d. *Technical Report on the Toxicity Studies of Carisoprodol (CAS No. 78-44-4) Administered by Gavage to F344/N Rats and B6C3F1 Mice*. National Toxicology Program. Research Triangle Park, NC. Accessed May 28, 2020 at http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox056.pdf.

NTP. 2004. *Monograph on the Potential Human Reproductive and Developmental Effects of Fluoxetine*. Center for the Evaluation of Risks to Human Reproduction, No. 05-4471, 2004. National Toxicology Program. Research Triangle Park, NC. Accessed May 28, 2020 at https://ntp.niehs.nih.gov/ntp/ohat/fluoxetine/fluoxetine_monograph.pdf.

NTP. 2008. Caffeine. National Toxicology Program Center for the Evaluation of Risks to Human Reproduction.

NTP. 2016. Norethisterone. In *14th Report on Carcinogens*. National Toxicology Program. Research Triangle Park, NC. Accessed May 28, 2020 at https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.

OEHHA. 2012. Final Statement of Reasons Title 27, California Code of Regulations Section 25705(b). Specific Regulatory Levels Posing No Significant Risk Tris (1,3-Dichloro-2-Propyl) Phosphate. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Accessed May 28, 2020 at https://oehha.ca.gov/media/downloads/crnr/100912fsortdcpp.pdf.

OEHHA. 2016. 2-Chloro-4,6-diamino-1,3,5-triazine. CASRN 3397-62-4. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Accessed May 28, 2020 at https://oehha.ca.gov/chemicals/2-chloro-46-diamino-135-triazine.

OEHHA. 2020a. 1,4-Dioxane. CASRN 123-91-1. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Accessed May 28, 2020 at https://oehha.ca.gov/chemicals/14-dioxane.

OEHHA. 2020b. 2-Amino-4-(isopropyl-d7-amino)-6-chloro-triazine. CASRN 6190-65-4. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Accessed May 28, 2020 at https://oehha.ca.gov/chemicals/2-amino-4-isopropyl-d7-amino-6-chloro-triazine.

OEHHA. 2020c. Proposition 65 No Significant Risk Levels (NSRLs) for Carcinogens and Maximum Allowable Dose Levels (MADLs) for Chemicals Causing Reproductive Toxicity. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Accessed May 28, 2020 at https://oehha.ca.gov/media/downloads/proposition-65//safeharborlist032519.pdf.

Ogata A, Ando H, Kubo Y, and Hiraga K. 1984. Teratogenicity of thiabendazole in ICR mice. *Food Chem Toxicol*. 22(7):509-520.

Panciera DL and Post K. 1992. Effect of oral administration of sulfadiazine and trimethoprim in combination on thyroid function in dogs. Can J Vet Res. 56(4):349-52.

Parravicini E, Fontana C, Paterlini GL, Tagliabue P, Rovelli F, Leung K, and Stark RI. 1996. Iodine, thyroid function, and very low birth weight infants. *Pediatrics*. 98(Pt 1):730-734.

Petrere JA, Humphrey RR, Anderson JA, Fitzgerald JE, and de la Iglesia FA. 1985. Studies on reproduction in rats with meclofenamate sodium, a nonsteroidal anti-inflammatory agent. *Fundam Appl Toxicol*. 5(4):665-71.

Pfizer. 2016. Drug label for Zithromax (azithromycin) 250 mg and 500 mg Tablets and Oral Suspension. Accessed May 28, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050710s44-050711s41-050784s28lbl.pdf.

Pfizer. 2018. Safety Data Sheet for Septra, Parkazole. Pfizer Pharmaceuticals Group, New York, NY. Accessed May 28, 2020 at https://www.pfizer.com/sites/default/files/products/material_safety_data/trimethoprim_sulfamethoxazole_tabs_21-aug-2018.pdf.

Pharmacia & Upjohn. 1995. Material Safety Data Sheet, Linco. MSDS, Pharmacia & Upjohn. Accessed May 28, 2020 at http://www.cvear.com/wp-content/uploads/2012/06/Lincomycin-inj.MSDS_.pdf.

Pizzi WJ, Alexander TD, and Loftus JT. 1996. Developmental and behavioral effects of prenatal primidone exposure in the rat. *Pharmacol Biochem Behav*. 55(4):481-7.

Quaile MP, Melich DH, Jordan HL, Nold JB, Chism JP, Polli JW, Smith GA, and Rhodes MC. 2010. Toxicity and toxicokinetics of metformin in rats. *Toxicol Appl Pharmacol*. 243(3):340-7.

Reddy JK and Qureshi SA. 1979. Tumorigenicity of the hypolipidaemic peroxisome proliferator ethyl-alpha-p-chlorophenoxyisobutyrate (Clofibrate) in rats. *Br J Cancer*. 40(3):476-482.

Roberts G. No date. Tiabendazole (Thiabendazole). World Health Organization. Accessed May 28, 2020 at http://www.inchem.org/documents/jecfa/jecmono/v31je04.htm.

Roche. 2012. Product label for EC-Naprosyn® (naproxen delayed-release tablets), Naprosyn® (naproxen tablets), Anaprox®/Anaprox® DS (naproxen sodium tablets), Naprosyn® (naproxen suspension). Roche Pharmaceuticals. U.S. FDA Center for Drug Evaluation and Research, Drugs@FDA. Accessed May 28, 2020 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017581s111,018164s061,018965s020,020067s018lbl.pdf.

RxList.com. 2019a. Professional Listing for Procardia (Nifedipine). RxList, The Internet Drug Index, RxList, Inc., San Clemente, CA. Accessed August 5, 2019 at http://www.rxlist.com/procardia-drug/warnings-precautions.htm.

RxList.com. 2019b. Professional Listing for Silvadene (Silver Sulfadiazine) topical. RxList, The Internet Drug Index, RxList, Inc., San Clemente, CA. Accessed August 5, 2019 at http://www.rxlist.com/silvadene-drug/warnings-precautions.htm.

RxList.com. 2019c. Professional Listing for Tegretol. RxList, The Internet Drug Index, RxList, Inc., San Clemente, CA. Accessed August 5, 2019 at https://www.rxlist.com/tegretol-drug.htm#description.

RxList.com. 2019d. Professional Listing for Fortamet. RxList, The Internet Drug Index, RxList, Inc., San Clemente, CA. Accessed August 5, 2019 at https://www.rxlist.com/fortamet-drug.htm

RxList.com. 2019e. The Internet Drug Index, RxList, Inc., San Clemente, CA. Accessed August 5, 2019 at https://www.rxlist.com/script/main/hp.asp.

Samren EB, van Duijn CM, Christiaens GC, Hofman A, and Lindhout D. 1999. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol*. 46(5):739-746.

Samren EB, van Duijn CM, Koch S, Hiilesmaa VK, Klepel H, Bardy AH, Mannagetta GB, Deichl AW, Gaily E, Granström ML, Meinardi H, Grobbee DE, Hofman A, Janz D, and Lindhout D. 1997. Maternal use of antiepileptic drugs and the risk of major congenital malformations: A joint European prospective study of human teratogenesis associated with maternal epilepsy. *Epilepsia*. 38(9):981-990.

Sant'Anna JR, Yajima JP, Rosada LJ, Franco CC, Prioli AJ, Della-Rosa VA, Mathias PC, and Castro-Prado MA. 2013. Metformin's performance in in vitro and in vivo genetic toxicology studies. *Exp Biol Med (Maywood).* 238(7):803-10.

SCCNFP. 2002. Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers, Concerning Salicylic Acid. Scientific Committee on Cosmetic Products and Non-Food Products. SCCNFP/0522/01. June. Accessed May 28, 2020 at http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out170_en.pdf.

Shepard TH and Lermire RT. 2004. *Catalog of Teratogenic Agents*. Johns Hopkins University Press, Baltimore, MD.

Silley P. 2007. Impact of antimicrobial residues on gut communities: are the new regulations effective? *J Appl Microbiol*. 102(5): 1220-1226. Accessed May 28, 2020 at https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2672.2007.03288.x.

Singh G, Driever PH, and Sander JW. 2005. Cancer risk in people with epilepsy: the role of antiepileptic drugs. *Brain*. 128(pt 1):7-17.

Soffritti M, Padovani M, Tibaldi E, Falcioni L, Manservisi F, Lauriola M, Bua L, Manservigi M, and Belpoggi F. 2016. Sucralose administered in feed, beginning prenatally through lifespan, induces hematopoietic neoplasias in male swiss mice. *Int J Occup Environ Health*. 22(1):7-17.

Stebbins RB and Coleman GL. 1967. A twenty-six month chronic toxicity study of GS-6244 in rats - dose levels of 100, 50 10, 5, or 0 mg/kg. Submitted to WHO by Pfizer Central Research. Groton, CT.

Toyoda T, Cho YM, Akagi JI, Mizuta Y, Matsushita K, Nishikawa A, Imaida K, and Ogawa K. 2018. A 13-week subchronic toxicity study of acetaminophen using an obese rat model. *J Toxicol Sci*. 43(7):423-433.

Ullah A, Ashraf M, Javeed A, Anjum AA, Attiq A, and Ali S. 2016. Enhancement of anti-proliferative activities of Metformin, when combined with Celecoxib, without increasing DNA damage. *Environ Toxicol Pharmacol*. 45:227-34.

U.S. EPA. 1987a. Bromacil Health Advisory. Office of Drinking Water. U.S. Environmental Protection Agency.

U.S. EPA. 1987b. p-Dioxane. Health Advisory. Office of Drinking Water. U.S. Environmental Protection Agency.

U.S. EPA. 1987c. Linuron. CASRN 330-55-2. Integrated Risk Information System. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0170_summary.pdf.

U.S. EPA. 1987d. N-Nitrosodimethylamine. CASRN 62-75-9. Integrated Risk Information System. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=45.

U.S. EPA. 1988a. Bisphenol A. CASRN 80-05-7. Integrated Risk Information System. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=356.

U.S. EPA. 1988b. Diuron. CASRN 330-54-1. Integrated Risk Information System. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0233_summary.pdf.

U.S. EPA. 1993. Simazine. CASRN 122-34-9. Integrated Risk Information System. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=263.

U.S. EPA. 1996. Registration Eligibility Decision (RED). Bromacil. United States Environmental Protection Agency.

U.S. EPA. 1998. Triclosan: Report of the Hazard Identification Assessment Review Committee. United States Environmental Protection Agency. October 22.

U.S. EPA. 2001. Toxicological Review of Quinoline, CASRN 91-22-5. In Support of Summary Information on the Integrated Risk Information System (IRIS). United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1004tr.pdf.

U.S. EPA. 2002. Reregistration Eligibility Decision (RED): Thiabendazole. U.S. Environmental Protection Agency. Washington, D.C. Accessed May 28, 2020 at https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-060101_1-May-02.pdf.

U.S. EPA. 2005a. Reregistration Eligibility Decision (RED) Document for Pyrazon. United States Environmental Protection Agency. Accessed May 28, 2020 at https://archive.epa.gov/pesticides/reregistration/web/pdf/pyrazon_red.pdf.

U.S. EPA. 2005b. Inert Reassessment of Methyl p-Hydroxybenzoate. United States Environmental Protection Agency. September 14.

U.S. EPA. 2008. Reregistration Eligibility Decision (RED) for Sulfometuron Methyl. United States Environmental Protection Agency. Accessed May 28, 2020 at https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-122001_18-Sep-08.pdf.

U.S. EPA. 2009. Provisional Peer-Reviewed Toxicity Values for Tris(2-chloroethyl)phosphate (TCEP) (CASRN 115-96-8). United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/pprtv/documents/Tris2chloroethylphosphate.pdf.

U.S. EPA. 2011. Exposure Factors Handbook. Office of Research and Development, United States Environmental Protection Agency. Washington, D.C. EPA/600/R-090/052F. September. Accessed May 28, 2020 at https://www.epa.gov/expobox/about-exposure-factors-handbook.

U.S. EPA. 2012c. Provisional Peer-Reviewed Toxicity Values for Tris(1-chloro-2-propyl)phosphate(CASRN 13674-84-5). November 29. United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/pprtv/documents/Tris1chloro2propylphosphate.pdf.

U.S. EPA. 2013. Toxicological Review of 1,4-Dioxane (With Inhalation Update)(CAS No. 123-91-1) In Support of Summary Information on the Integrated Risk Information System (IRIS). United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf.

U.S. EPA. 2014. Provisional Peer-Reviewed Toxicity Values for Perfluorobutane Sulfonate (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3). United States Environmental Protection Agency. Accessed May 28, 2020 at https://cfpub.epa.gov/ncea/pprtv/documents/PotassiumPerfluorobutaneSulfonate.pdf.

U.S. EPA. 2016. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). United States Environmental Protection Agency. Accessed May 28, 2020 at https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf.

U.S. EPA. 2020. National Primary Drinking Water Regulations. United States Environmental Protection Agency. Accessed May 28, 2020 at https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations

USPC. 2007. Monograph on Sulfonamides (Veterinary- systemic). U.S. Pharmacopeial Convention. Accessed May 28, 2020 at https://cdn.ymaws.com/www.aavpt.org/resource/resmgr/imported/sulfonamides.pdf.

Vyas A, Purohit A, and Ram H. 2018. Assessment of dose-dependent reproductive toxicity of diclofenac sodium in male rats. *Drug Chem Toxicol*. 2:1-9.

WA DEQ. 2020. CLARC data tables and other technical information. State of Washington Department of Ecology. Accessed May 28, 2020 at https://ecology.wa.gov/Regulations-Permits/Guidance-technical-assistance/Contamination-clean-up-tools/CLARC/Data-tables.

WHO. 1990. ADI for Acesulfame K. Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva. Accessed May 28, 2020 at http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=3613.

WHO. 1996. 2,4-D. CASRN 94-75-7. Joint Meeting on Pesticide Residues (JMPR). World Health Organization. Geneva. Accessed May 28, 2020 at https://apps.who.int/pesticide-residues-jmpr-database/pesticide?name=2%2C4-D.

WHO. 1999. Estradiol-17beta. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva. Accessed May 28, 2020 at https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=1835.

WHO. 2000. Lincomycin. In: *Toxicological Evaluation of Certain Veterinary Drug Residues in Food. WHO Food Additive Series 45*. Fifty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization. Geneva. Accessed May 28, 2020 at http://www.inchem.org/documents/jecfa/jecmono/v45je02.htm.

WHO. 2004. Lincomycin. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization. Geneva. Accessed May 28, 2020 at http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=4170.

WHO. 2006. Propyl paraben, addendum. Prepared by S. Barlow, A. Mattia, and J-C. Leblanc. In: Safety evaluation of certain food additives and contaminants. WHO Food Additives 58. World Health Organization. Geneva. Accessed May 28, 2020 at https://apps.who.int/iris/bitstream/handle/10665/43645/9789241660587_eng.pdf?sequence=1.

Yamada T, Maita K, Nakamura J, Murakami M, Okuno Y, Hosokawa S, Matsuo M, and Yamada H. 1994. Carcinogenicity studies of oxolinic acid in rats and mice. *Food Chem Toxicol*. 32(5):397-408.

Yoshimura H. 2002. Teratogenic assessment of carbadox in rats. *Toxicol Lett*. 129(1-2):115-118.

Zoetis. 2016. ALBON- sulfadimethoxine tablet. Drug product label. Accessed May 28, 2020 at https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=71a27a8a-038b-4b6d-8237-d6b58ddf9dc8&type=display