U.S. Fish & Wildlife Service

ECOLOGICAL HAZARD ASSESSMENT OF CONTAMINANTS OF EMERGING CONCERN IN THE U.S. GREAT LAKES BASIN

Part B - Supplemental Document:

Technical Resources for Ecological Hazard Assessments of Contaminants of Emerging Concern in Freshwater Fish

September 2019

Biological Technical Publication

BTP-R3018-2019

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Executive Summary

Contaminants of emerging concern (CECs) comprise a diverse and growing group of principally anthropogenic chemicals in commerce that are generally poorly understood with respect to fate, transport, and toxic effects in ecological systems. They include tens of thousands of personal care products, flame retardants, new pesticides, pharmaceuticals, hormones, veterinary drugs, fragrances, food additives, surfactants, and many other chemicals contained in commercial products. Many CECs are ubiquitous in surface waters. Analytical methods have been developed for detecting hundreds of individual CECs in ambient waters. Yet, few official agency guidelines or benchmarks exist for CECs in surface waters in the United States (U.S.) and few CECs are regulated as environmental contaminants.

The principal purpose of this document is to present the rationale, derivation methods, and numeric values of CEC screening values (SVs) for assessing relative hazard to freshwater fish from chronic aqueous exposures in surface water, to aid in improving management strategies for fish and wildlife resources. The SVs presented here are neither regulatory values nor absolute toxicity thresholds. The USFWS does not establish national regulatory screening values for contaminants, and estimation of absolute toxicity thresholds was not a goal of this project.

We developed pairs of effect-specific SVs and mean SVs for each of the 14 CECs to be used as guidance values in aquatic ecological hazard assessments (EHAs) concerning freshwater fish. A SV_{LOW} is a CEC concentration in water below which minimal adverse impacts to fish populations are anticipated. A SV_{HIGH} is a water concentration above which adverse impacts in fish are expected. The SVs are intended to be applied as pairs to score relative hazard of aqueous CEC exposures. Resulting hazard scores can be used to rank hazard and prioritize among alternative research and resource management actions concerning the potential for CEC impacts in freshwater systems. This approach combines the merits of lower bound SVs (concentrations below which impacts are not anticipated) with the merits of upper bound SVs (concentration above which impacts are reasonably expected) in interpreting CEC hazard.

The process of deriving pairs of SVs generated additional resources for ecological hazard assessment. A comprehensive CEC Fish Ecotoxicity Database was compiled for this project from published laboratory assays on single-CEC effects in freshwater fish from chronic aqueous exposures. The structure and contents of this database directly supported derivation of SVs for the 14 CECs. Uncertainty factors (UFs) related to six sources of uncertainty were developed to adjust for lab-to-field extrapolation in CEC SV derivations. The UFs were applied to NOAECs to derive SV_{LOW} point estimates, and applied to LOAECs to derive SV_{HIGH} point estimates. Complete lists of SV point estimates with associated UFs and assay information are provided in Attachments and summarized in CEC-specific SV point estimate distribution graphs. We developed effect-specific SVs from SV point estimates related to individual Effect Categories - such as Mortality, Reproductive, Developmental, Behavioral, and eight other categories of effects. Effect-specific SVs were then used to compute the mean SV values.

Two pairs of mean SVs were developed from effect-specific SVs for each CEC. A set of comprehensive SV_{HIGH} and SV_{LOW} values were developed using all adverse effects reported in the literature for a given CEC. A subset of adverse effects was used to derive a set of population-relevant SV_{HIGH} and SV_{LOW} values, to focus EHAs on the potential for population-level impacts.

We recommend applying all available effect-specific SVs and mean SVs in each EHA to take full advantage of their interpretive power. To illustrate the magnitude of the derived SVs, we provide mean SV values below:

CEC	Use	Comprehensive		Population-relevant	
		SV_{HIGH} µg/L	SV_{LOW} µg/L	SV_{HIGH} µg/L	SV_{LOW} µg/L
4-Androstene-3,17-dione	Hormone	0.852	0.000204	3.23	0.00127
Bisphenol A	Plasticizer	118	0.0318	177	0.062
Carbamazepine	Pharmaceutical - anticonvulsant	139	0.00865	299	0.0788
Citalopram	Pharmaceutical - antidepressant	0.222	0.000102	0.237	0.000254
N,N-diethyl-meta-toluamide (DEET)	Insect repellant	22	0.0236	7098	0.00127
Diphenhydramine	Pharmaceutical - antihistamine	1.26	0.00846	3.35	0.0527
Estrone	Hormone	0.00665	0.0000144	0.0186	0.000115
Hexahydrohexamethyl cyclopentabenzopyran	Personal Care - fragrance - musk	21.3	0.0649	60.2	0.91
Ibuprofen	Pharmaceutical – antiinflammatory (NSAID)	10.5	0.0153	0.822	0.00417
Lidocaine	Pharmaceutical - antiarrhythmic	890	2.4	949	5.98
β-Sitosterol	Phytohormone	18.4	0.0604	101	0.171
Tris(2-butoxyethyl)phosphate (TBEP)	Flame retardant	267	0.448	511	1.67
Triclosan	Personal Care - antibacterial	12.8	0.00254	40.8	0.00286
Venlafaxine	Pharmaceutical - antidepressant	0.155	0.000638	0.285	0.0026

Limitations of the SVs presented in this document include:

- The SVs are not regulatory values.
- The SVs are not absolute thresholds of toxicity.
- SVs for only 14 CECs are presented; hazards due to exposures to other CECs are not addressed in this document
- The SVs are applicable to freshwater fish, only; relevance to other taxa is unknown.
- The SVs are applicable for chronic or long-term repeated exposure scenarios, only; relevance to acute exposures is unknown.
- The SVs are relevant to aqueous exposures, only; SVs do not account for trophic intake
  - SVs are best compared to concentrations in dissolved phase in surface water samples, not total concentrations.
  - Hazard due to CECs with relatively high $\log K_{ow}$ values will likely be underestimated compared to CECs with low $\log K_{ow}$ values.

Acknowledgements

The USFWS Great Lakes CEC ecological hazard assessment and CEC screening value development were funded by the Great Lakes Restoration Initiative through the USFWS's CEC Team.

We appreciate continued encouragement and technical support from the USFWS CEC Team, past and present: Mandy Annis, Dr. Amber Bellamy, Steve Choy, and Zach Jorgenson. In particular, we thank the CEC Project management team – Dr. Annette Trowbridge and Dr. Stephanie Hummel, without whom this work would not have been possible. Additional USFWS colleagues who contributed substantively to concepts and content in this document include: Dr. Amy Roe, Dr. Lisa Williams, and Dr. Kathleen Patnode. We are grateful to the U.S. Geological Survey and SGS AXYS Analytical for providing current detection limits of emerging contaminants.

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Background

The U.S. Fish and Wildlife Service (USFWS) is conducting a Contaminants of Emerging Concern Project in the Great Lakes Basin to determine if these mostly unregulated chemicals negatively impact fish and wildlife. This project addresses the Great Lakes Restoration Initiative Action Plan II, Objective 1.2.2: *Identify emerging contaminants and assess impacts on Great Lakes fish and wildlife.* The USFWS is evaluating the influence of these novel and potentially toxic substances on the health of the fish and wildlife in the Great Lakes Basin. This work is conducted under the statutory authority of the Great Lakes Fish and Wildlife Restoration Act, and is funded under the Great Lakes Restoration Initiative through the USFWS's CEC Team.

The first five years of the project, implemented during 2010-2014, resulted in an improved understanding of the occurrence patterns of many CECs in water and sediment in Great Lakes tributary rivers as well as a preliminary identification of some chemicals likely to adversely affect fish (Choy et al. 2017, Elliott et al. 2017, Lee et al. 2012, Lee et al. 2015, Thomas et al. 2017). The second five years is aimed at determining whether the most common CECs and their mixtures may affect the growth, survival, or reproduction of individuals and the sustainability of fish and wildlife populations.

This document is Part B in a two-part report on the USFWS Great Lakes Basin Ecological Hazard Assessment (EHA) concerning impacts to fish populations from exposures to CECs. The full EHA is provided in Part A (Gefell et al. 2019). Part A is an illustration of how to apply CEC screening values to score CEC concentrations in water for hazard to fish populations; hazard scores were used to rank CECs and project locations distributed throughout the U.S. Great Lakes Basin for relative hazard to fish populations.

Part B supplements Part A by presenting a detailed treatment of the EHA Toxicity Assessment, in particular the derivation of CEC screening values. Part B also supports future CEC EHAs by providing an assortment of technical resources for ecological risk assessment practitioners. Assessment resources presented in this document provide a technical basis for prioritizing future research and resource management related to CECs in aquatic systems of the Great Lakes Basin.

Acronym List

ACR	Acute to Chronic Ratio
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criterion
BPA	Bisphenol A
CAS	Chemical Abstract Service
CCME	Canadian Council of Ministers of the Environment
CEC	Contaminant of Emerging Concern
CECWG	Chemicals of Emerging Concern Working Group
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CFED	CEC Fish Ecotoxicity Database
DEET	N,N-diethyl-metatoluamide
DNEL	Derived No-Effect Level
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EHA	Ecological Hazard Assessment
EML	Effect Magnitude at the LOAEC
ECOSAR	Ecological Structure-Activity Relationships model
EPUC	Effect per Unit Concentration
ERA	Ecological Risk Assessment
ET	Ecotoxicity Threshold
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
HHCB	Hexahydrohexamethyl-cyclopentabenzopyran
IJC	International Joint Commission
LC_{50}	50% Lethality Concentration
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
MDL	Method Detection Limit
MF	Modifying Factor
MRL	Minimal Risk Level
NLM	National Library of Medicine
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NYSDEC	New York State Department of Environmental Conservation
OPP	Office of Pesticide Programs
OSWER	Office of Solid Waste and Emergency Response
PAH	Polycyclic Aromatic Hydrocarbon
PCB	Polychlorinated Biphenyl
PEC	Predicted Exposure Concentration
PNEC	Predicted No Effect Concentration
QSAR	Quantitative Structure-Activity Relationship
QSPR	Quantitative Structure-Property Relationship
RfD	Reference Dose
SAR	Structure-Activity Relationship
SARA	Superfund Amendments and Reauthorization Act
SLERA	Screening Level Ecological Risk Assessment
SSD	Species Sensitivity Distribution
SV	Screening Value
SV_{HIGH}	LOAEC-derived Upper CEC Screening Value
SV_{LOW}	NOAEC-derived Lower CEC Screening Value
TBEP	Tris(2-butoxyethyl) phosphate
TRV	Toxicity Reference Value
UF	Uncertainty Factor
UF_{CC}	Chemical Complexity Uncertainty Factor
UF_{Conc}	Effect Concentration Uncertainty Factor
UF_{Data}	Database Adequacy Uncertainty Factor
UF_{Dura}	Exposure Duration Uncertainty Factor
UF_{Inter}	Inter-Species Sensitivity Uncertainty Factor
UF_{Intra}	Intra-Species Sensitivity Uncertainty Factor
$UF_{\prod}$	Cumulative Uncertainty
UNEP	United Nations Environmental Programme
USEPA	U.S. Environmental Protection Agency
USFWS	U.S. Fish and Wildlife Service
USGS	U.S. Geological Survey

Chapter 1 - Introduction

1.1 Purposes

The principal purposes of this document are to:

- Provide a companion document to Part A (Gefell et al. 2019), describing the Toxicity Assessment process used to derive CEC SVs for fish (Figure 1-2);
- Provide information to ecological assessment practitioners, natural resource managers, and water managers:
    - a synthesis of CEC fish ecotoxicity information for 14 commonly detected CECs
    - a set of technical resources to conduct EHAs that:
        - assess relative hazard to freshwater fish in order to prioritize sites for further attention,
        - rank CECs for relative hazard to aquatic resources.
- Provide detailed methods that can be applied to derive new CEC SVs or update existing SVs.

Other important purposes include:

- Increase field sampling efficiency and simplicity for CEC hazard assessment in fish
- Provide an opportunity to assess the potential for CEC impacts extensively at a landscape scale, such as across watersheds or basins
- Minimize future euthenization of fish to assess potential hazards, by:
    - providing an alternative to traditional field sampling for pathology studies in fish health assessments;
    - providing a thorough review of available laboratory studies so future laboratory investigations can focus on critical data gaps, and avoid redundant studies, especially related to CECs.

Technical resources provided in this document include:

- a database on effects of CECs in fish (Chapter 2),
- a set of uncertainty factors for extrapolating CEC effect concentrations from lab to field conditions (Chapter 3), and
- a set of surface water screening values for aqueous exposure[1] of 14 CECs in freshwater fish (Chapter 4).

Brief introductions to these project outputs are provided in Sections 1.4 – 1.6.

1.2 Terminology

Emerging contaminants are recognized as a global issue (UNEP 2010, UNEP 2014). The Great Lakes International Joint Commission (IJC) Chemicals of Emerging Concern Work Group provides the following description (CECWG 2011):

> *The term "chemicals of emerging concern" has come to characterize the increasing awareness of the presence in the environment of many chemicals used by society, and the risk they may pose to humans and ecosystems... Chemicals of emerging concern include new compounds that have gained entry into the environment or those that have been recently characterized due to increases in concentrations in the environment or improvements in analytical techniques. In the United States and Canada few of these compounds have regulations governing their release. Of concern is the uncertainty of potential adverse effects on wildlife and humans due to chronic exposure to low concentrations of these compounds.*

For the purposes of this document, the term *contaminants of emerging concern* is used interchangeably with *emerging contaminants*, where the word "emerging" can refer to our limited knowledge and control, as well as to new uses and our recent ability to detect these chemicals in the environment. Emerging contaminants include a wide

[1]Throughout this document, the phrase "aqueous exposure" refers principally to direct uptake of dissolved chemical from water – that is, uptake via the gills and integument and ingestion of water. In assays that last long enough so that the fish are fed, there may also be some uptake via ingestion of food particles to which the tested CEC has adsorbed. The degree of adsorption and, hence, the potential importance of this route of exposure is influenced by chemical properties of the food particles and the tested CEC.

variety of chemicals in commerce (Chapman 2006, Howard and Muir 2010, Howard and Muir 2011, UNEP 2010), including pharmaceuticals, veterinary drugs, personal care products, flame retardants, surfactants, plasticizers, hormones, fragrances, new biocides, and other categories. Very few CECs are regulated with respect to their release into the environment (CECWG 2009), yet a very large number of these compounds (thousands) were specifically designed to be biologically active.

In comparison, with the exception of pesticides, *legacy contaminants* were designed for purposes other than biological activity. Many legacy contaminants are compounds that are well-characterized with respect to their ecotoxicity and fate, have been used and discharged to the environment for decades, and/or are no longer used in commerce but may persist in the environment at concentrations of concern. Some examples are polychlorinated biphenyls (PCBs), dioxins, polycyclic aromatic hydrocarbons (PAHs), metals such as mercury, cadmium, and chromium, chlorinated pesticides such as DDT and its derivatives, and many others. The fate and effects of most legacy contaminants are well known, and many are known to be toxic. Many of these well-studied legacy chemicals have been regulated for decades. Legacy contaminants are included in the U.S. Environmental Protection Agency (USEPA) Priority Pollutant List (USEPA 2016a), which is a priority subset of the USEPA "list of lists" of regulated hazardous substances (USEPA 2015a). Legacy contaminants are not included in the current report.

Chemical ecological risk assessments (ERAs) are simplified analyses of the potential for chemical impacts in complex ecological systems. In risk assessment, the word "risk" implies a quantitative estimate of the *probability* of adverse effects, given the exposures, while the word "hazard" implies a more qualitative *potential* to cause harm (Suter 1993). In this sense, an assessment that is often called a screening level ERA (SLERA) is also known as an ecological hazard assessment (EHA), which is the term used throughout this document. The fish ecotoxicity database, uncertainty factors, and screening values provided in this document were developed for use in EHAs concerning relative hazard to freshwater fish from exposure to aqueous CECs.

Historically, a number of screening values have been developed to satisfy federal or state statutory or regulatory requirements related to legacy contaminant levels in surface water (see Table 1-1). We refer to these values as *regulatory* SVs. Other screening values presented in Table 1-1 are *non-regulatory*, which have been developed to provide additional, but unenforceable, guidance to ecological risk assessors with respect to hazard to aquatic organisms from contaminant exposures.

The USFWS provides the CEC SVs in this document as guidance values for research and resource management decision-making and prioritization between alternative actions; the SVs provided herein are neither regulatory nor enforceable.

1.3 Technical Background

Methods for EHAs have been developed for both prospective (e.g., USEPA 2004, ECB 2003) and retrospective (e.g., USEPA 1997, USEPA 2001) scenarios. Prospective EHAs are conducted in advance of circumstances that may result in exposures of ecological receptors to contaminants or prior to measuring environmental concentrations of contaminants. Prospective EHAs make assumptions about potential environmental exposures, including the use of modeled concentrations. For example, prospective EHAs may be applied to screen new pesticides and other chemicals, before manufacturing, for their potential to cause negative ecological impacts (e.g., von der Ohe et al. 2011), to screen existing pesticides under new exposure circumstances (USEPA 2004), or to screen existing chemicals in commerce for monitoring prioritization (e.g., Arnot et al. 2006, Howard and Muir 2010, Howard and Muir 2011). Retrospective EHAs evaluate the potential for adverse effects in ecological receptors in locations where chemicals are already present in the environment (Suter 1993), usually at measurable concentrations. At hazardous waste sites, a retrospective EHA is often used to focus the chemical and spatial scope of remediation or future contaminant monitoring or other field studies by screening chemicals and sampling locations for relative hazard potential to ecological receptors (USEPA 2001). Retrospective EHAs are often used to identify locations, exposure pathways, and USEPA priority contaminants (or other regulated legacy contaminants) that pose negligible

risks (USEPA 1997) and thus can be deemphasized in the subsequent baseline ecological risk assessment.

Classic elements of a chemical hazard assessment - exposure assessment, toxicity assessment, and hazard characterization (Figure 1-1) – are shared among EHA applications used by various environmental agencies. Specific terminology varies between environmental agencies, but concepts are similar. A common technical thread tying the four elements together is the development of a conservative estimate of relative hazard based on a comparison (usually the ratio) between exposure and an exposure-effects threshold. Exposure is represented as either a predicted or measured metric, such as probable exposure concentration (PEC), maximum or mean exposure point concentration, or body burden. Predicted threshold levels of toxicity may be either protective of, or suggestive of, adverse effects - such as, probable no-effect concentration (PNEC), toxicity reference value (TRV), ambient water quality criterion (AWQC), or ecotoxicity threshold (ET) (see Table 1-1). Units of the exposure and toxicity metrics must be the same, resulting in a unitless hazard quotient. Conceptually, the simplest hazard quotient compares measured environmental concentrations (e.g., mean, maximum) against a toxicologically relevant threshold level of exposure in the same medium.

This document provides a detailed description of CEC screening values (SVs) for aquaeous exposures. It is Part B of a two-part series. The first document (Part A) is an EHA concerning the potential for CEC impacts to Great Lakes fish, which refers to this document (Part B) for details on the Toxicity Assesment. We define SVs as estimated concentrations of chemicals in water that demarcate our expectations about adverse effects in target biota. Emerging contaminant SVs are derived by applying uncertainty factors (UFs) to effect concentrations provided in a CEC Fish Ecotoxicity Database. The database, UFs, and SVs are introduced briefly in the following sections.

1.4 Effects Databases

Our process of deriving screening values began with a comprehensive compilation of published laboratory studies on CEC effects in fish. In published fish CEC assays, aqueous exposure assays predominate. Publications were sought that concerned fish ecotoxicity in 25 CECs that were among the most frequently detected in water samples collected across the Great Lakes Basin during 2010-2012 in the USFWS Great Lakes CEC project (Attachment 1-1; Choy et al. 2017).

Four separate databases of CEC effects information in fish were compiled from the literature. These are described in detail in the following sections of this document. The principal database is the CEC Fish Ecotoxicity Database, which was structured to generate SV point estimates from CEC effect concentrations (Lowest Observed Adverse Effect Concentrations (LOAECs) and No Observed Adverse Effect Concentrations (NOAECs)) (see Chapter 2). The other three databases are structured to derive empirical uncertainty factors (UFs) (see Chapter 3): Chemical Complexity UF (UF_{CC}); Inter-Species Sensitivity UF (UF_{Inter}); and Intra-Species Sensitivity UF (UF_{Intra}).

All four of these databases are in Microsoft Excel 2010 flat file format.

1.5 Uncertainty Factors

Screening EHA applications commonly include an explicit, quantitative or quasi-quantitative, accounting for one or more sources of uncertainty. These sources of uncertainty are associated with extrapolations of laboratory experimental exposure-effect results to expectations of effects under field conditions (e.g., USEPA 1997). Sources of uncertainty in EHAs involving legacy contaminants have been reviewed in the literature (e.g., Chapman et al. 1998, Duke and Taggart 2000), but UF values for deriving SVs for CECs have not yet been described for applications in the U.S. This distinction will be discussed further in Chapter 3.

Chapter 3 describes the rationale, derivation process, and application guidance for six sources of uncertainty that were accounted for to derive CEC SVs:

1. Chemical Complexity (aka Mixture) – empirically derived (Section 3.2)
2. Inter-Species Sensitivity – empirically derived (Section 3.3)
3. Intra-Species Sensitivity – empirically derived (Section 3.4)
4. Exposure Duration – professional judgement based on literature (Section 3.5)
5. Effect Concentration (LOAEC-to-NOAEC) Extrapolation – professional judgement based on literature (Section 3.6)
6. Database Adequacy – professional judgement based on literature (Section 3.7)

The sixth UF, Database Adequacy, is applied at a different point in the process than the first five UFs listed above, which comprise the Cumulative UF (see Figure 1-2). The concept of Cumulative Uncertainty is explained in Section 3.8. Finally, Section 3.9 introduces the concept of a Modifying Factor (MF). The MF was not used to derive any SVs in this report, but practitioners may use an MF to further adjust SVs based on their specific application.

1.6 CEC Screening Values

Screening values are estimated concentrations of chemicals in water that delineate our expectations about adverse effects in target biota. Pairs of SVs

were developed for CECs that were detected frequently in U.S. Great Lakes Basin surface waters (see Chapter 4). One of the SVs identifies a level of exposure below which negligible hazard to fish is expected (i.e., the SV is protective against adverse effects), and the other SV indicates a level of exposure above which there is a reasonably high expectation of hazard (i.e., the SV is suggestive of adverse effects). These are SV_{LOW} and SV_{HIGH}, respectively. Concentrations falling between the SVs represent an intermediate but less certain hazard level; an absolute toxicity threshold likely falls between the SV_{LOW} and SV_{HIGH}, but its specific value is unknown and likely varies with receptor and exposure conditions. The pair of SVs efficiently summarizes relevant information contained in the CFED for the purpose of scoring relative hazard, and ultimately for ranking hazard among sampled sites and among CECs. The companion document (Part A) provides a detailed example of application of SVs in an ecological hazard assesment. Further, for each CEC, two sets of SVs were derived for EHA applications – the first set of SVs focuses on conventional population-relevant effects, and the second set of SVs is comprehensive, utilizing all available effects information (Figure 1-2).

Population-relevant effects of CEC exposure that are observed in closed laboratory assays are likely not the same as those occurring in the open environment, where immigration, emigration, compensatory reproduction, multiple stressors, and other factors are also influencing population dynamics. Yet, ecotoxicity assay results provide a reasonably reliable foundation for describing the degree to which individual CECs (or specific CEC mixtures) may affect population parameters.

A variety of ecotoxicological benchmarks have been developed for legacy contaminants under various programs and for various regulatory applications (Suter 1996, DOE 1996). Table 1-1 compares features of existing surface water SVs, mostly for legacy contaminants, against USFWS SVs for CEC exposures in fish.

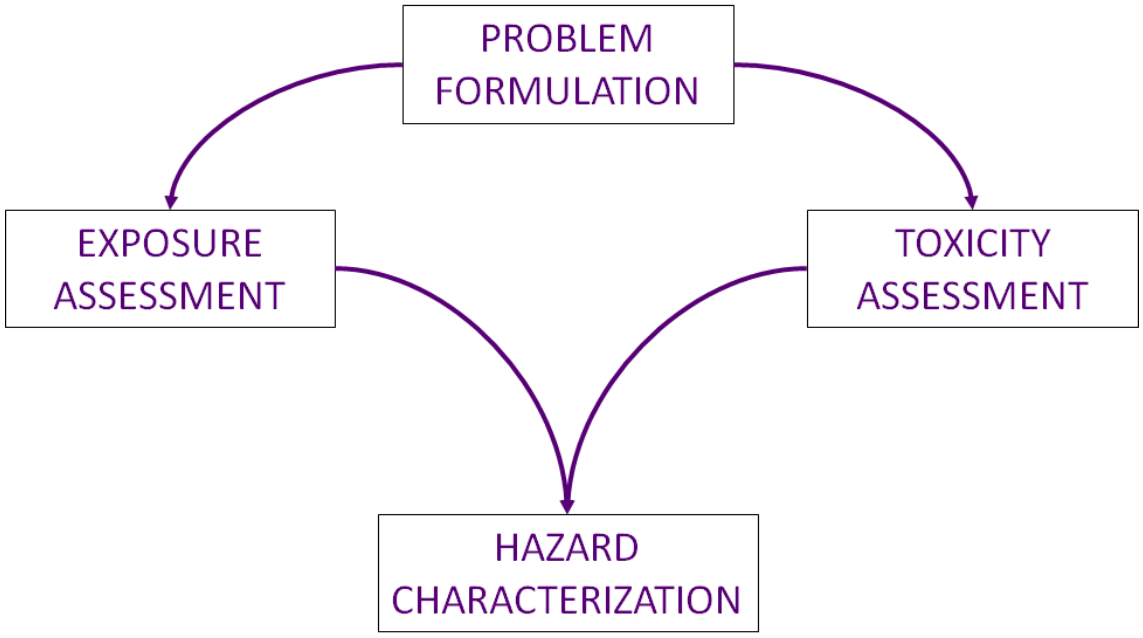


Figure 1-1. Classic elements of a chemical ecological hazard assessment

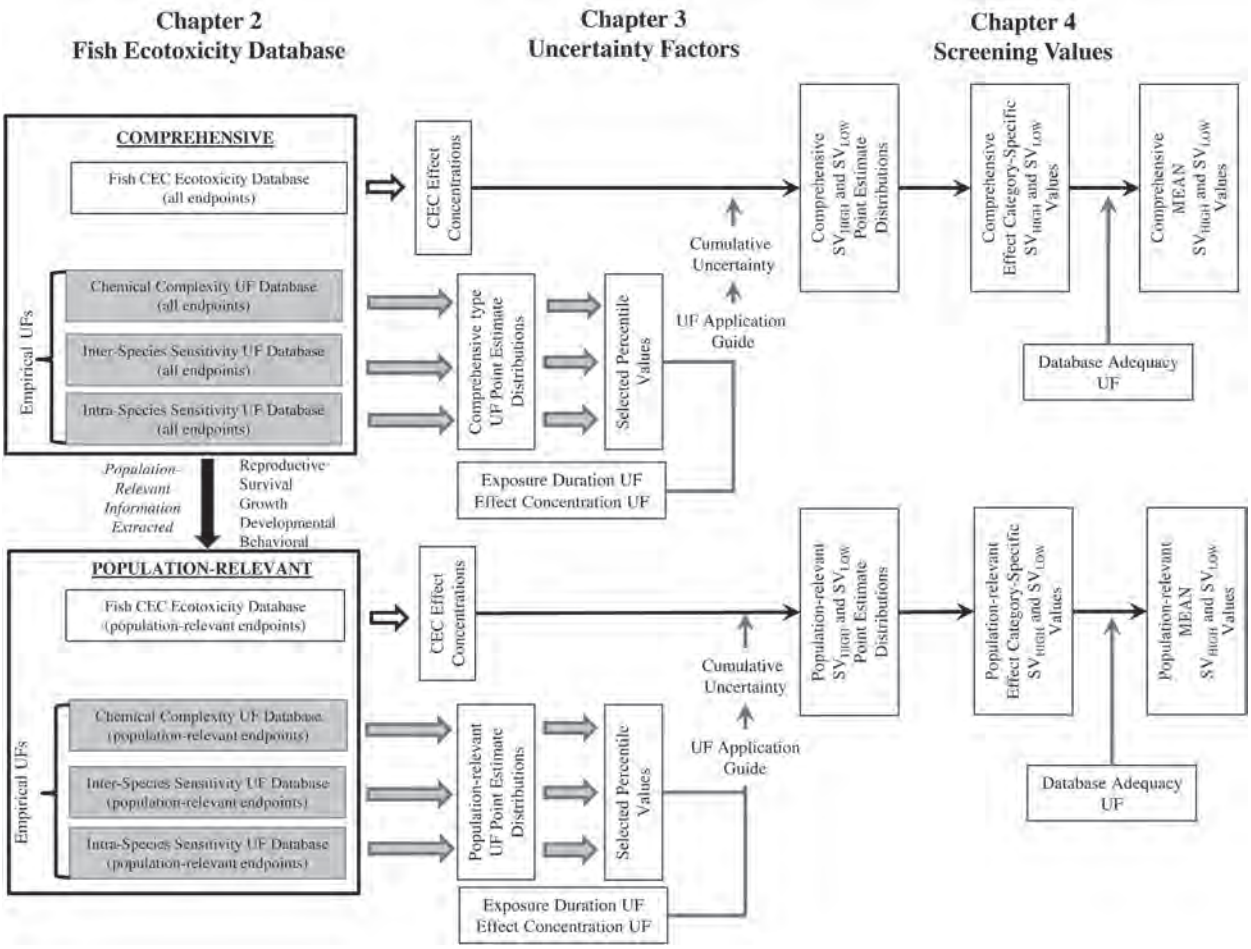


Figure 1-2. Summary diagram illustrating inter-relationships among the three tool sets developed in this project for CEC toxicity assessment in fish EHAs: CEC ecotoxicity databases, uncertainty factors, and screening values for CECs in water. Database elements related to empirical uncertainty factor derivation are shaded.

Table 1-1. Attributes of SV values developed in this document (*shaded*) compared to selected surface water ecotoxicity screening value derivation programs; see Suter (1996) and DOE (1996) for more comprehensive treatment of ecotoxicity screening values, including from individual states.

Name	Abbreviation	Regulatory Threshold and/or Enforceable (Y/N)	Government	Program/ Authority(ies)	Agency/ Office	Meaning	Application	Exposure Duration in studies used to derive	Water Filtration	Taxa	Legacy Contaminants or CEC application	Allows Modeled Exposure or Effects Data	Reference
CEC Screening Values	**SV_{HIGH} and SV_{LOW}**	**N**	**United States**	**USEPA Great Lakes National Program Office's (GLNPO) Great Lakes Restoration Initiative (GLRI); Fish and Wildlife Restoration Act**	**USFWS**	**PAIR:** • **SV_{LOW} - Concentration *below which* adverse impacts to fish *are not expected*, and** • **SV_{HIGH} - Concentration *above which* adverse impacts to fish *are expected***	**Retrospective hazard assessment; Potential prospective applications; surface waters**	**Chronic, or chronic-equivalent (adjusted from acute or subchronic)**	**Filtered Water**	**Fish[2]**	**CECs only**	**No**	**This Report**
Aquatic Life Ambient Water Quality Criterion – Criterion Continuous Concentration	AWQC - CCC	Y	United States	Clean Water Act	USEPA, Office of Water	"…the highest concentration of specific pollutants or parameters in water that are not expected to pose a significant risk to the majority of species in a given environment…"	Retrospective hazard assessment; surface waters	Chronic	Organics – unfiltered; metals - filtered	aquatic life	Legacy – primarily priority pollutants; only one or two CECs to date	No	USEPA 1985; USEPA 1993a; USEPA 2016b

[2]This document describes USFWS SVs for fish; we anticipate developing additional SVs for other taxonomic groups as availability of quality ecotoxicity information allows.

Table 1-1. (continued)

Name	Abbreviation	Regulatory Threshold and/or Enforceable (Y/N)	Government	Program/ Authority(ies)	Agency/ Office	Meaning	Application	Exposure Duration in studies used to derive	Water Filtration	Taxa	Legacy Contaminants or CEC application	Allows Modeled Exposure or Effects Data	Reference
Great Lakes Initiative, Water Quality Criterion – Criterion continuous concentration	WQC - CCC	Y	United States	Clean Water Act	USEPA, Office of Water	"…an estimate of the highest concentration of a material in the water column to which an aquatic community can be exposed indefinitely without resulting in an unacceptable effect."	Retrospective hazard assessment; surface waters	Acute, Chronic	Organics – unfiltered; metals – filtered	aquatic life	Legacy	No	USEPA 1993a; USEPA 1995
Ecotox Threshold	ET	N	United States	CERCLA / SARA	USEPA, OSWER	Concentration "above which there is sufficient concern regarding adverse ecological effects to warrant further site investigation"	Retrospective hazard assessment; hazardous waste sites	Acute, Chronic	Unfiltered water for organics; filtered water for metals	aquatic life	Legacy	Un-specified	USEPA 1996a
Ecological Screening Values	ESV	N	United States	CERCLA / SARA	USEPA, Region 4 Super-fund Division	"…chemical concentrations associated with a low probability of unacceptable risks to ecological receptors."	Retrospective hazard assessment; hazardous waste sites	Acute, Chronic	Un-specified	aquatic life	Legacy	Yes	USEPA 2015b

Table 1-1. (continued)

Name	Abbreviation	Regulatory Threshold and/or Enforceable (Y/N)	Government	Program/ Authority(ies)	Agency/ Office	Meaning	Application	Exposure Duration in studies used to derive	Water Filtration	Taxa	Legacy Contaminants or CEC application	Allows Modeled Exposure or Effects Data	Reference
Aquatic Life Benchmarks	N/A	N	United States	FIFRA	USEPA, OPP	"…concentrations below which pesticides are not expected to harm aquatic life"; benchmarks are used "to identify and prioritize sites and pesticides that may require further investigation"	Prospective hazard assessment; Pesticide Registration Programs	Acute, Chronic	Un-specified	Fish, Inverte-brates, Plants	Legacy and newer pesticides	Un-specified	USEPA 2004
Water Quality Guidelines	WQG	N	Canada	Canadian Water Quality Guidelines	Environ ment Canada	"…maximum concentrations of substances…in the aquatic ecosystem that are intended to protect all forms of aquatic life (all species, all life stages) for indefinite exposure periods."	Retrospective hazard assessment; surface waters	Chronic	Unfiltered, unless otherwise specified	All aquatic life forms	Legacy and some CECs	No	CCME 1999; CCME 2007a
Probable No Effects Concentration	PNEC	?	European Union	•Commission Directive 93/67/EEC; •Commission Regulation (EC) No 1488/94; •Directive 98/8/EC	Various	"…the concentration below which unacceptable effects on organisms will most likely not occur"	Prospective hazard assessment	Acute, Chronic	Un-specified	varies	Both	Yes	ECB 2003

Chapter 2 - CEC FISH ECOTOXICITY DATABASE

2.1 Introduction

A CEC Fish Ecotoxicity Database (CFED) was developed for deriving SVs for surface water CEC exposures in fish. Information for the database was extracted from the primary literature rather than relying on data reported in secondary sources. Primary publications were identified using the USEPA ECOTOX database (USEPA 2016c) and the National Library of Medicine (NLM) TOXLINE database (NLM 2016). Additional primary sources were identified using Google Scholar and bibliographies in retrieved publications.

The purpose of the CFED is to support development of CEC-specific pairs of SVs for ranking relative hazard in fish from aqueous CEC exposures. The structure of the database leads directly into the approach to derive SVs. Details on SV derivation are provided in Chapter 4. The first step in the SV derivation process is to develop a set of CEC-specific SV point estimates derived from effect concentrations reported in each CFED record (Figure 2-1).

2.2 Literature Inclusion Criteria

This section describes quality assurance guidelines to ensure consistent data acquisition procedures and data quality. Contents of the current version of the CFED include assays with the following attributes:

- *Receptor Group*: Fish species that live at least part of their life cycle as facultative or obligate freshwater habitat residents.
- *Chemical Scope*: Database contents are limited at this time to information on commonly detected CECs (Choy et al. 2017; (Attachment 1-1) for which ecotoxicity information in the peer-reviewed literature was sufficient to derive a pair of SV values (see Chapter 4).
- *Ecotoxicity Study Design:* Only laboratory experiments that included a negative (water and/or vehicle) control group were included, as appropriate.
- *Exposure Duration:* Studies in which fish were continuously or repeatedly (i.e., renewal) exposed to CECs for subchronic (7 to 28 days) or chronic (>28 days) exposure durations were included, as well as studies where the exposed life stage or measured effect endpoint occurs for a shorter duration. The rationale for duration categories is provided in Section 3.5 – Exposure Duration.
- *Exposure Complexity:* Single-CEC exposures, only.
- *Exposure Route:* Only in vivo exposure studies are included. Aqueous exposure to CECs (concentration in water is reported as the exposure metric), which includes:
    - Direct uptake from water via the gills, or integument
    - Incidental ingestion of water, and
    - Incidental ingestion of CECs adhered to food, in longer studies that include feeding the fish.
- *Effect Concentration:* Effect concentrations included in the CFED are the following: bounded LOAEC, bounded NOAEC, unbounded LOAEC, unbounded NOAEC, bounded LOEC, unbounded LOEC, bounded NOEC, or unbounded NOEC (see definitions in Section 2.4.1). These effect concentrations were identified from reported statistical comparisons against a negative control group. If included in the study design, a vehicle control group was the preferred negative control. Otherwise, a water negative control group was used. Only LOAEC and NOAEC values were used to derive SVs. Measured and nominal test concentrations were identified in separate fields; measured values were used preferentially to derive SVs. See Section 2.4 for Effect Concentration definitions and rationale. See Section 3.6 for incorporation of nominal/measured concentration distinction into uncertainty factors.
- *Effect Category:* Only effect categories described in Section 2.5 and Attachment 2-1 were entered into the database. Lists of specific endpoints evaluated in studies included in the database are provided in CEC-specific sections in Chapter 4 (Sections 4.4.1 – 4.4.14).
- *Publication Type:* With very few exceptions (that were identified in the database), only primary publications in peer-reviewed journals reporting quantitative empirical results from controlled experiments were included. No modelled effects data were included.
- *Publication Language:* English, only.

- *Publication Date:* The current version of the database includes primary literature located in database searches conducted through July, 2016; any studies published prior to that date, that satisfy the constraints listed above, were considered.

2.3 CEC Fish Ecotoxicity Database Structure

The CFED is an Excel spreadsheet in flat-file format (MS Excel v. 14.0.7172.5000 (32-bit)). Database information is organized into five groups: Reference, Chemical, Receptor, Exposure, and Effects.

The following list identifies the fields included in each group; groups and fields are presented in the database in this order:

Reference Information
- Primary Author, Last
- Primary Author, First
- Other Authors, Last (List)
- Year
- Full Title
- Full Citation
- Keywords as Indicated in Publication
- Peer-reviewed (P) or gray (G) literature

Chemical Information
- Common Chemical Name
- CAS Number
- CEC Category
- Exposure Medium

Receptor Information
- Target Taxa
- Species Common Name
- Scientific Name
- Ecological System
- Life Stage(s) of Exposed Fish
- Sex of Exposed and Evaluated Fish
- Residence in Great Lakes Basin

Exposure Information
- Exposure Location (Lab, Mesocosm)
- Single Chemical Exposure (Y/N)[3]
- Mixture Exposure (Y/N)
- Nominal Exposure Concentrations – List
- Mean Measured Exposure Concentrations – List
- Reported Exposure Concentration Units
- Exposure Concentration Notes
- Exposure Duration
- Reported Exposure Duration Units

Effect Information
- LC_{50} or EC_{50}[4]
- LOEC
- NOEC
- LOAEC (unbounded)
- LOAEC (bounded)
- NOAEC (bounded)
- NOAEC (unbounded)
- Frank Effect (Y/N)
- Multiple Stressor Study (Y/N)[5]
- Population-Relevant[6] Endpoint(s) (Y/N)
- Effect Category
- LOAEC Effects Observed and NOAEC

Effects Reported
- LOEC Effects Observed

2.4 Guidelines for Effect Concentration

An effect concentration is a concentration in water that is associated with a particular response level reported in a publication for a specific effect endpoint. Effect concentrations for both adverse and other effect endpoints are recorded in the database. Adverse effect concentrations (LOAECs and NOAECs) are the starting points for SV derivations.

2.4.1 Effect Concentration Definitions

Working definitions for specific effect concentrations to represent published data consistently in the CFED are the following:

- *Lowest Observed Adverse Effect Concentration (LOAEC)* is the lowest concentration tested in a controlled laboratory study at which an adverse effect was statistically significantly greater (i.e., worse, in terms of adverse effect prevalence or intensity) than the same effect in the control group. "Adverse" effects are direct negative impacts either to the health and survival of the exposed fish itself (e.g., oxidative stress, serum hormone levels, renal necrosis, reduced predator avoidance, aberrant growth and development, or mortality) or the function of the individual in propagation (e.g., reduced gamete viability, reduced nesting rates, reduced hatching rates, or increased malformations in offspring).

[3]Although only single-chemical exposure studies are included in this version of the database, mixture studies may be added in subsequent versions.
[4]No acute toxicity information is included in this version of the database, but may be in later versions.
[5]Neither mixture study data, nor information concerning non-chemical stressors, are currently included in the database, although the database may include those types of results in the future.
[6]The term "population-relevant" here does not refer to attributes of populations, such as intrinsic rate of increase or finite rate of increase. Rather, it simply means that at least one of the effect endpoints (all of which are measured at the individual fish level of organization) that are associated with the effect concentration is readily interpretable with respect to population modeling (see Section 2.5). Population-relevant endpoints are described in Figure 2-2 and in Attachment 2-1.

- An *"Unbounded" LOAEC* is the lowest tested concentration at which adverse effects were demonstrated by statistical comparison to controls, and it is the lowest test concentration in the study.
- *A "Bounded" LOAEC* is the lowest tested concentration at which adverse effects were demonstrated by statistical comparison to controls, but there were lower concentrations tested in the study at which no adverse effects were demonstrated statistically.
- LOAECs are assigned by Effect Category in each study, not for each individual adverse effect endpoint. For example, one publication may provide LOAEC values for several adverse reproductive endpoints for a given CEC, but only the lowest LOAEC among those endpoints is recorded in the CFED. The word "Reproductive" would be entered into the Effect Category field for that record, and the numeric value of the lowest LOAEC among the reproductive endpoints is entered into the appropriate field. The breadth of specific endpoints and exposure constraints that define each Effect Category are defined in Attachment 2-1.
- The following exceptions in assigning LOAECs were used:
  - Some CECs may have non-monotonic, non-linear exposure-response curves. We accounted for this possibility as follows. Even if a statistically significant difference from the control is observed at a particular exposure concentration, no LOAEC is identified if no significant adverse effects were observed for the same endpoint at any higher exposure level.
  - A LOAEC may be identified even in the absence of tabulated or graphical statistical comparisons to controls. The authors may either identify an effect concentration in the text or report a statistically significant trend in response on exposure. Also, a graph that does not identify statistically significant differences among groups still may be confidently interpreted by inspection to illustrate a significant difference - for example, differences that may be visually conveyed by inspection of error bars, intercepts, and reported slopes.

- *No Observed Adverse Effect Concentration NOAEC)* is the highest concentration tested in a study at which no adverse effects could be demonstrated by statistical comparison to a control group. As with LOAECs in the database, only one NOAEC may be identified for an Effect Category in a given study. The breadth of endpoints and exposure constraints that define each Effect Category are defined in Section 2.5 and Attachment 2-1.
  - *An Unbounded NOAEC* is the highest tested concentration, where no adverse effect is demonstrated at any exposure concentration by statistical comparison to a negative (vehicle and/or water) control group.
  - *A Bounded NOAEC* is the highest exposure concentration at which no effects were observed, where the next higher exposure concentration is the corresponding Bounded LOAEC.

- *Bounded and Unbounded No Observed Effect Concentrations* (NOECs) and *Bounded and Unbounded Lowest Observed Effect Concentrations* (LOECs) are similar to the NOAECs and LOAECs, except that the endpoints evaluated are provisionally considered to be not "adverse". For instance, effects not recorded as adverse in the database include (but are not limited to) the following: enzyme activation, altered hepatosomatic index, reduced RNA transcription, reduced mRNA expression, and increased gene expression. Some effects that were not recorded in this evaluation as adverse may in fact be linked to clearly adverse effects via an adverse outcome pathway, but the strength of linkage to an adverse outcome is not clear. Other effects recorded as NOECs and LOECs may be regarded as indicators of exposure rather than indicators of toxicity. See Attachment 2-1 for further discussion of the distinction between adverse and other effects, as well as designations by effect category.

- ECx[7] (e.g., EC_5, EC_{20}, EC_{50}) identifies an estimated exposure concentration (EC) that would result in specified adverse effects in "x" percent of exposed individuals.
  - The *LCx* is a special case of an ECx, where the effect endpoint is lethality.
  - Calculation of an ECx/LCx requires measured responses at multiple measured exposure concentrations.

[7]ECx and LCx values are effect concentrations usually computed from results of acute exposure studies. While none of these values are included in the current version of the fish ecotoxicological database, their definitions are included here for completeness.

2.4.2 Rationale for Effect Concentrations

For decades there has been discussion in the ecotoxicity literature advocating the abandonment of effect concentration metrics that rely on statistical hypothesis testing to identify LOAEC/LOEC and NOAEC/NOEC values (e.g., Chapman and Caldwell 1996, Jager 2012, Kooijman et al. 1996, Laskowski 1995). A key objection to the use of NOAEC/NOEC values is that even though the difference in effect magnitude may not be statistically significant between an exposure group and a negative control (which is more likely to occur as sample size decreases and/or variance increases), it does not mean that a significant biological effect has not occurred due to contaminant exposure. Others have proposed a transition to different metrics based on empirical models. For example ECx values, which are effect concentrations (EC) associated with specific response percentiles (x), are estimated from regression analysis of a given effect endpoint (e.g., Hanson and Solomon 2002, Hoekstra and Van Ewijk 1993, Landis and Chapman 2011, van der Hoeven et al. 1997, Warne and van Dam 2008).

Despite the interest among many ecotoxicologists to move beyond statistical hypothesis-based effect concentration metrics (LOAEC/LOEC and NOAEC/NOEC) we have compiled these metrics in the CFED and utilized LOAEC/NOAEC values in SV derivations. We chose this approach based on the following pragmatic reasons:

- A vast majority of studies published in the primary literature on emerging contaminant effects in fish report results of statistical tests for differences in response between various exposure levels and a negative control, by effect endpoint, generating LOEC/LOAEC and/or NOEC/NOAEC values.
- Studies that report ECx values for effects after chronic exposures in fish are rare, and different studies do not necessarily report ECx values at the same response percentile (x).
- Studies published in journals typically do not report regression equations appropriate for estimating ECx values or supply supporting files with the original datasets from which to derive regressions.
- Acquiring original datasets, acquiring permission to use the data, and performing regression analyses for each endpoint in each study in the CFED would require a prohibitively massive effort that has precluded systematically contacting individual authors for their datasets.

2.4.3 Assigning Effect Concentrations

Both nominal and measured exposure levels were recorded in the CFED, but measured concentrations were used preferentially as the Effect Concentrations to derive SVs. Nomimal concentrations were used as Effect Concentrations only when measured exposure levels were not reported. Uncertainty associated with the use of nominal concentrations to derive SVs was addressed in the Effect Concentration Uncertainty Factor (Section 3.6). Modeled effect concentrations were not included in the database or in SV derivations.

The CFED records are uniquely distinguished among each other by Reference, Chemical, Receptor, Exposure, and Toxic Effects information (Section 2.3; Figure 2-1). Individual publications are identified by the reference fields. The study design is comprised of the chemical, receptor, and exposure fields. Study results are captured in the effects fields, including Effect Concentrations. A single publication may report results from multiple assays with different study designs and effects, resulting in several CFED records (see Figure 2-1).

Effect Concentrations from a specific publication/study design are recorded in the CFED according to the following guidelines:

- Either one or two records exist in the database for each Effect Category reported from an individual publication/study design.
- For a given Effect Category in a given publication/study design, Effect Concentrations for endpoints not explicitly identified as adverse (i.e., LOEC and/or NOEC) are provided in a record separate from that recording the adverse Effect Concentrations.
- All of the adverse endpoints for a single Effect Category from a given publication/study design are presented in a single record, and the lowest LOAEC among the grouped endpoints is provided in that record.
    - If the LOAEC is bounded, then the corresponding bounded NOAEC for that endpoint is also reported in the same record.
    - If no LOAEC is available for a given Effect Category with effect endpoints that were evaluated in the publication/study design, then the highest unbounded NOAEC among the endpoints evaluated is recorded in the database for that Effect Category.

Under certain circumstances, an Effect Concentration of an endpoint that is not designated as a population-relevant Effect Concentration may have been used as

a proxy for a population-relevant Effect Concentration to derive population-relevant SV point estimates (see Figure 2-2 for population-relevance concept). In these cases, a suborganismal LOAEC may be antecedent to population-relevant effects within an adverse outcome pathway. For instance, a LOAEC in an adverse endpoint that is not considered population-relevant (e.g., altered serum reproductive hormone levels) may be an indicator of related but not statistically significant population-relevant effects (e.g., reduced egg production per female).

Only adverse Effect Concentrations (LOAECs or NOAECs) were used in the derivation of SV point estimates, and a single CFED record may contribute Effect Concentrations toward derivation of up to four types of SV point estimates (see Section 4.3.2; Figure 4-2): population-relevant SV_{HIGH}, population-relevant SV_{LOW}, comprehensive SV_{HIGH}, and comprehensive SV_{LOW}.

2.5 Guidelines for Effect Categories and Assigning Population-relevance to Effect Endpoints

Each effect concentration in the database is associated with one effect category. Effect categories include Behavioral, Developmental, Growth, Reproductive, and other groupings of effect endpoints. Guidelines were developed to ensure consistent assignment of study results to effect categories, and to assist database users with locating information in the database. The guidelines, provided in Attachment 2-1, are aligned with common human health and ecological effects terminology.

Consistent application of the effect category guidelines is important for consistent SV derivations. Effect category is one of the fields that differentiates between database records. At least one SV point estimate was generated for each CFED record that reports either a LOAEC or NOAEC. No SVs were derived from NOECs or LOECs. See Chapter 4 for details on deriving SV point estimates from effect concentrations.

The distinction between population-relevant and comprehensive SVs is based partly on the Effect Category field (Figure 1-2; Figure 2-2). See Attachment 2-1 for more detail and rationale for effect endpoints that we designated as population-relevant.

The number of effect categories represented in the CFED for a given CEC also provides a gross indication of the adequacy of the database for that CEC. Values of the Database Adequacy UF are assigned based on the premise that the greater the number of effect categories, the greater confidence that critical effect concentrations for the CEC are identified. For each CEC, effect-specific SVs were derived that may be used for custom hazard assessments in which only certain categories of effects are of interest (see Section 4.3.3). Effect-specific SVs are the inputs to deriving CEC-specific mean SVs (see Sections 4.3.4 and 4.4). The Database Adequacy UF is used during the calculation of mean SVs from effect-specific SVs. Tables 3-16 and 3-17 provide the basis for assigning the Database Adequacy UF - a breakdown of numbers of records in the database that were used to derive SVs, by CEC and Effect Category.

2.6 Database Applications

The principal purpose of the CFED is to summarize CEC ecotoxicity information from the peer-reviewed literature, organized to facilitate derivation of CEC SVs. Database records are uniquely distinguished among each other by Reference, Chemical, Receptor, Exposure, and Toxic Effects information (Figure 2-1). The database structure leads directly into the first step in SV derivation, which is to produce a distribution of SV point estimates for each CEC. The CFED includes adverse (LOAEC/NOAEC) and other (LOEC/NOEC) effect concentrations from a single assay in separate database records. Although, only effect concentrations for adverse effect endpoints (LOAECs/NOAECs) are used to compute SV point estimates. All of the adverse effect data related to one Effect Category from a single published assay is summarized in one CFED record.

Population-relevant adverse effect concentrations (Figure 2-2, Attachment 2-1) are used to develop both population-relevant and comprehensive SVs. A single CFED record may contribute between one and four SV point estimates, depending on the Effect Category and type(s) of effect concentration reported in that record (Table 2-1). For instance, if a bounded LOAEC/NOAEC pair is recorded in a CFED record for a population-relevant adverse effect endpoint, that record produces four SV point estimates: population-relevant SV_{LOW} and SV_{HIGH}, and comprehensive SV_{LOW} and SV_{HIGH} (see Figure 4-2). However, for CFED records with Effect Concentrations representing other adverse effect endpoints, only comprehensive SV_{LOW} and/or comprehensive SV_{HIGH} point estimates may be derived.

The database is also useful as a quick reference for researchers and resource managers who seek fish toxicity information for CECs.

2.7 Quality Assurance/Quality Control

We relied on the scientific peer-review process to vet the quality of published information that we summarized in the CFED. All data included in the database were obtained from peer-reviewed publications (with rare exceptions, which were noted and justified). Data entry from published papers followed consistent guidelines. Where interpretation of published information was required, explicit guidance was provided both for consistent data entry and for quality control – for example, see guidance provided in Sections 2.4 and 2.5, and Attachment 2-1. Iterative reviews of the accuracy of the database were conducted following data entry.

Reference Information	Chemical Information	Receptor Information		Exposure Information		Toxicity Information	
		Species	Life Stage	Duration	Exposure Concentrations	Effect Category	Effect Concentration
Paper 1	CEC 1	Species 1	Embryo	4 days	0, 1, 10, 100 ug/L	*DEVELOPMENTAL*	Unbounded NOAEC
			Adult	4 days		*BEHAVIORAL*	Unbounded LOAEC
				28 days		*SURVIVAL*	Bounded LOAEC/NOAEC
						Gross Pathology	Bounded LOAEC/NOAEC
				65 days	0, 0.01, 0.1, 1 ug/L	*GROWTH*	Unbounded LOAEC
						Neurological	Unbounded LOAEC
						DEVELOPMENTAL	Bounded LOAEC/NOAEC
		Species 2	Juvenile, Adult	7 days	0, 1, 10, 100 ug/L	Genetic	Bounded LOAEC/NOAEC
						REPRODUCTIVE	Bounded LOAEC/NOAEC
	CEC 2	Species 2	Larva	7 days	0, 25, 500, 750 ng/L	*DEVELOPMENTAL*	Unbounded NOAEC
			Adult	81 days	0, 0.25, 5, 7.5 ng/L	*BEHAVIORAL*	Unbounded LOAEC
						SURVIVAL	Bounded LOAEC/NOAEC
						REPRODUCTIVE	Bounded LOAEC/NOAEC
	CEC 3	Species 3	Juvenile, Adult	7 days	0, 50, 150, 500 ug/L	Histopathology	Bounded LOAEC/NOAEC
						SURVIVAL	Unbounded LOAEC
Paper 2	CEC 3	Species 1	Juvenile, Adult	25 days	0, 0.01, 0.1, 1 ug/L	*GROWTH*	Bounded LOAEC/NOAEC
						SURVIVAL	Unbounded LOAEC
						REPRODUCTIVE	Bounded LOAEC/NOAEC

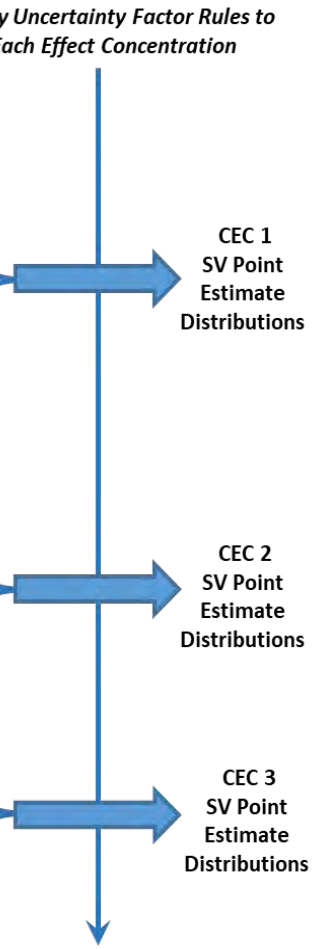


Figure 2-1. Schematic illustration of how exposure-effects data are parsed from published papers into separate database records, which feeds directly into the first step in SV derivation – development of SV point estimate distributions for each CEC. Comprehensive type SVs utilize all effect categories, while population-relevant SVs are based on population-relevant endpoints in certain effect categories (highlighted in bold, italic caps). In this illustration, two papers contributed a total of 18 records for three CECs; 14 of the records pertain to population-relevant effects

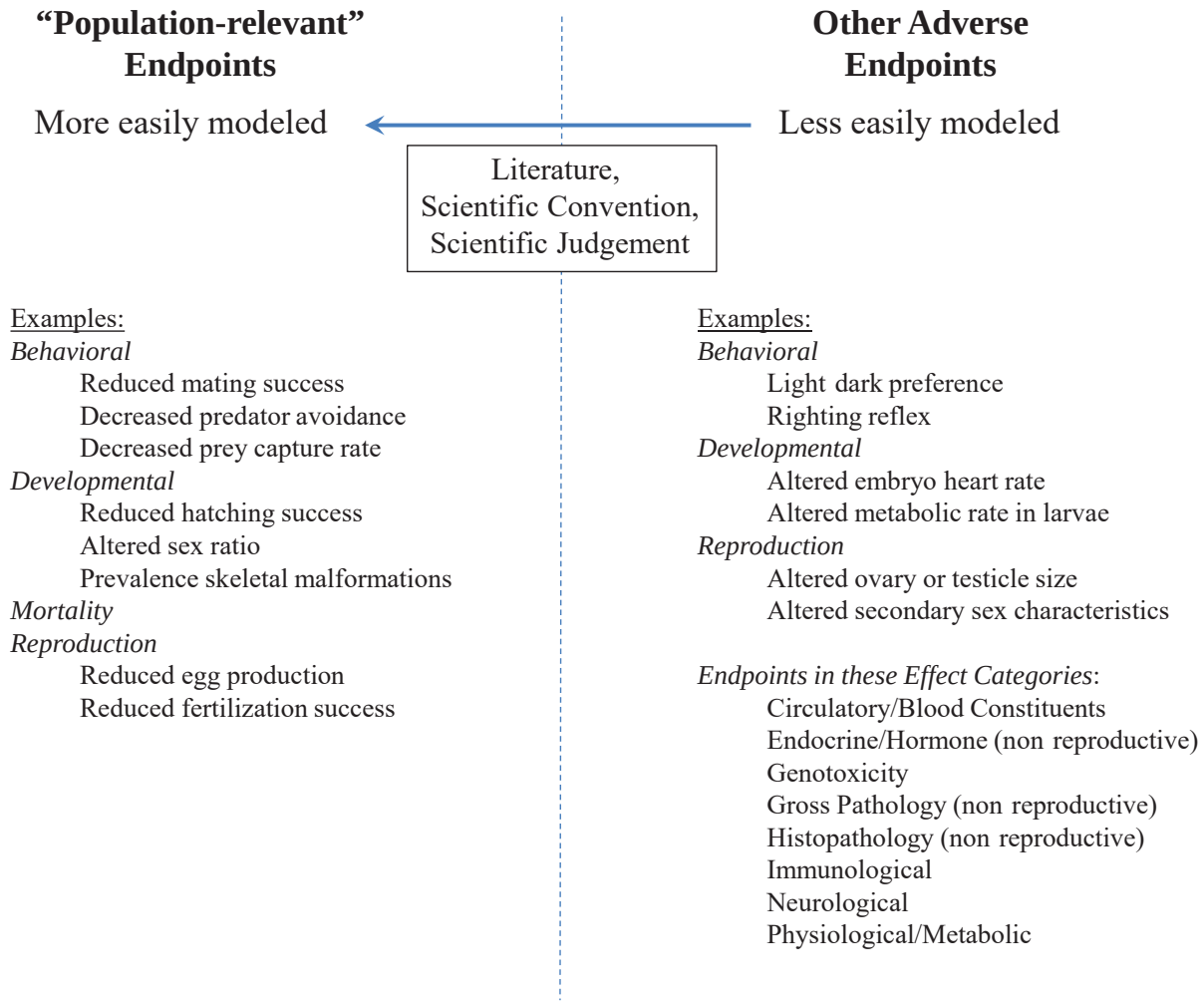


Figure 2-2. Schematic illustration of designation of "population-relevant" effect endpoints. We defined population-relevant effect endpoints as those effect data that are readily incorporated into a quantitative, mechanistic population dynamics model. Derivation of "population-relevant" SVs used population-relevant endpoints, while derivation of "comprehensive" SVs included all adverse endpoints (both population-relevant and other).

Table 2-1. Types of Screening Value point estimates produced from specific combinations of effect endpoint (Section 2.5; Attachment 2-1) and effect concentration (Section 2.4) reported in individual records of the CEC Fish Ecotoxicity Database (CFED).

Type of Effect Endpoint	Type of Effect Concentration	Type(s) of SV Point Estimate(s)[8]
Population-relevant Adverse Effects	Unbounded NOAEC	Population-relevant SV_{LOW} Comprehensive SV_{LOW}
	Unbounded LOAEC	Population-relevant SV_{LOW} and SV_{HIGH} Comprehensive SV_{LOW} and SV_{HIGH}
	Bounded NOAEC/LOAEC Pair	Population-relevant SV_{LOW} and SV_{HIGH} Comprehensive SV_{LOW} and SV_{HIGH}
Population-relevant Other Effects	NOEC and/or LOEC	None
Non-Population-relevant Adverse Effects	Unbounded NOAEC	Comprehensive SV_{LOW}
	Unbounded LOAEC	Comprehensive SV_{LOW} and SV_{HIGH}
	Bounded NOAEC/LOAEC Pair	Comprehensive SV_{LOW} and SV_{HIGH}
Non-Population-relevant Other Effects	NOEC and/or LOEC	None

[8]Although the NOAEC is the principal toxicological basis for deriving SV_{LOW} values, SV_{LOW} point estimates were also derived from Unbounded LOAEC values by applying an uncertainty factor to adjust the effect concentration (UF_{Conc}) to obtain an estimated NOAEC (refer to Section 3.6).

Chapter 3 - UNCERTAINTY FACTORS for EMERGING CONTAMINANTS

3.1 Purpose and Background

The purpose of this chapter is to provide rationale, derivation methods, application guidance, and numeric values for the uncertainty factors (UFs) that were used to derive CEC SVs. Uncertainty factors were used to adjust laboratory CEC effect concentrations (NOAECs, LOAECs) to estimate an environmental CEC water concentration with comparable effect levels in sensitive target species and life stages. The role of UFs in development of population-relevant SVs and comprehensive SVs is depicted in Figure 1-2. Practitioners may apply the full set of UFs and guidelines reported in this chapter to derive SV point estimates for additional CECs.

Assessment of chemical impacts to ecological receptors in dynamic environmental exposure scenarios requires simplifying assumptions in order to maintain tractability of the problem. In aquatic systems there are typically many possible receptor species, with widely divergent life histories, which may be directly affected by chemical exposures. Each potential receptor species may also be indirectly impacted via contaminant-caused alterations in the food web, habitat, or other critical aspects of the receptors' aquatic ecosystem. There are often numerous chemical contaminants, multiple sources of chemical contamination, and contaminants having varying rates of degradation and bioaccumulation, and that partition differently between aquatic media. Hence, each potential receptor population is usually exposed via multiple exposure pathways to a complex mixture of chemicals.

The totality of chemical exposures cannot be known, since standardized analytical methods do not exist for the vast majority of probable contaminants (and their metabolites and degradation products). In aquatic systems, exposure levels vary spatially and temporally, and uptake varies among receptor organisms and environmental conditions. Depending on the mobility and life history of potential receptors relative to the spatial distribution of toxic contaminants, receptors may be exposed episodically for only a few brief periods, continuously or repeatedly throughout their lifetime, or over many generations.

Non-toxic stressors (e.g., water temperature, suspended sediment, dissolved oxygen, pH, nutritional deficiencies, and predation) are also continuously affecting organisms directly. Aquatic environment factors such as dissolved oxygen concentration, water temperature, and salinity have been shown to modify contaminant uptake or susceptibility of receptors to effects from chemical exposure, including CECs (e.g., Matson et al. 2008, Park et al. 2011, Waring and Moore 2004). Non-chemical stressors may vary widely, particularly in the gradients upstream to downstream of urban areas, or in temperate zones with large seasonal changes.

In contrast to the complexity of real aquatic systems, reliable lab-based ecotoxicological information is limited to effects from a very small fraction of possible chemical contaminants – usually a single contaminant - in relatively few receptors, and within a physiologically favorable, controlled range of non-contaminant stressor conditions. Further, toxicity assessments in screening level EHAs for legacy contaminants typically utilize criteria, standards, or other toxicity screening values that were derived using organismal (*individual*) level data[9] reported in lab studies, but practitioners are often concerned with the potential for impacts to wild *populations*.

Clearly, there is uncertainty as to the direct relevance of laboratory-derived aquatic ecotoxicological information to chemical impacts in real aquatic systems. When attempting to extrapolate from lab to real-world scenarios, uncertainty is often organized into categories, and UFs are developed for each category. Simplifying assumptions are unavoidable in these extrapolations.

[9]Assessment endpoints may be defined and quantified at one or more ecological levels of organization:

- individual organism (e.g., survival, age at sexual maturity, physiological stress, immunological competence, hematological balance, etc.);
- population (e.g., absolute or relative abundance, intrinsic or finite rate of increase, sex ratio, age distribution, life table structure, etc.).

3.1.1 Historical UF Use in Legacy Contaminant EHAs

A variety of UFs have been used historically to derive ecological screening values for EHA applications at hazardous waste sites contaminated with legacy chemicals (e.g., USEPA's priority contaminant list). Values of UFs depended on the specific application (Table 3-1).

Researchers have described the historical evolution of methods development in, and the experimental underpinnings of, UF applications in human health risk assessment (HHRA) for non-carcinogenic chemicals (e.g., Dourson and Stara 1983, Dourson et al. 1996, Dourson and Parker 2007, Simon et al. 2016). As with other aspects of chemical risk assessment, the use of UFs in developing screening values for EHAs is patterned after the logic developed for HHRAs for legacy contaminants. Environmental regulatory agencies have provided guidance to account for various sources of uncertainty in EHAs involving contaminants (e.g., USEPA 1997, USEPA 2001).

Types of extrapolation UFs include chemical complexity (UF_{CC}), Inter-species extrapolation (UF_{Inter}), Intra-species extrapolation (UF_{Intra}), Exposure Duration (Acute to Chronic) (UF_{Dura}) and Effect Concentration extrapolation (LOAEC to NOAEC) (UF_{Conc}). When more than one UF category has been addressed in an EHA, UF values have usually been multiplied together to represent cumulative uncertainty. This method of combining sources of uncertainty is described in human health risk assessment guidance (USEPA 1989) and has been adopted as common practice in applied ERAs (Duke and Taggert 2000). An implicit assumption in the multiplication of UF values is that sources of uncertainty are independent of each other. An SV is computed by dividing an effect concentration (NOAEC or LOAEC) by cumulative uncertainty. Dividing an effect concentration by the product of UFs is the equivalent of dividing the starting effect concentration by each individual UF, sequentially, as in:

$$SV = (((((NOAEC / UF_{CC}) / UF_{Inter}) / UF_{Intra}) / UF_{Dura}) / UF_{Conc})$$

Thus, UFs have been used to adjust critical effect concentrations from lab studies into conservative estimates of effect concentrations in a real aquatic system, resulting in an SV value that is conservatively protective.

3.1.2 UFs for CECs

Many CECs, including a majority of those CECs that have been studied in fish ecotoxicity assays reported in the literature, have been developed purposely to have strong biological activity. These include pharmaceuticals, veterinary drugs, synthetic hormones, and new herbicides, fungicides, pesticides, and antimicrobials. This is in contrast to most legacy contaminants, for which strong biological activity is most often incidental to the purpose for which the chemical was designed – with the exception of legacy biocides such as DDT or Toxaphene. It is plausible, therefore, that variability in response to contaminant exposure, and uncertainties in extrapolating from the lab to the environment, may differ between classic legacy contaminants and CECs. While UFs have been extensively applied in EHAs involving legacy contaminants (Table 3-1), UF values specifically for deriving screening values for aqueous CECs have not been described by U.S. environmental agencies.

We developed CEC UFs and suggested guidelines for the following sources of uncertainty related to extrapolating laboratory-derived effect concentrations to environmental exposures relevant intended for screening:

- *Chemical Complexity* (UF_{CC}) (Section 3.2) - adjusts single-CEC effect concentrations (LOAECs or NOAECs) in water that were reported in a controlled laboratory study to an exposure scenario involving the same CEC in a mixture;
- *Inter-Species Sensitivity* (UF_{Inter}) (Section 3.3) - adjusts a LOAEC or NOAEC from a controlled laboratory study that tested for effects in a single species to an estimated effect concentration in a receptor species or group of species that are more sensitive to the subject CEC;
- *Intra-Species Sensitivity* (UF_{Intra}) (Section 3.4) - adjusts a LOAEC or NOAEC from a controlled laboratory study that tested for effects in one class of individuals within a fish species to an estimated effect concentration in a more sensitive class of individuals in the same species;
- *Exposure Duration* (UF_{Dura}) (Section 3.5) - adjusts a LOAEC or NOAEC from a controlled laboratory study that tested for effects after acute or subchronic exposures to a presumed equivalent effect concentration after chronic exposure;
- *Effect Concentration* (UF_{Conc}) (Section 3.6) - adjusts an unbounded LOAEC to an estimated corresponding NOAEC for the same CEC, endpoint, species, life stage, and exposure route and duration, including adjustment for nominal exposure concentrations reported in lab studies;
- *Database Adequacy* (UF_{Data}) (Section 3.7) - adjusts the mean SV for uncertainty associated with limited quantity and breadth of reliable and available ecotoxicity information

Derived UF point estimates, descriptive information about source studies, and literature citations for source data are tabulated in Attachments identified in the following sections.

3.1.3 UF Usage for CEC SV Derivation

Uncertainty factors were used to derive CEC SV point estimates. Each record in the CFED generated at least one SV point estimate (see Chapter 2). The CEC UFs we present in Chapter 3 were used to derive SV point estimates from effect concentrations (NOAECs or LOAECs) in each record of the CFED. We developed guidelines to assign a specific numeric value for each type of UF, depending on the type of SV being derived (comprehensive or population-relevant) and/or the study design associated with the particular Effect Concentration. For instance, the numeric value of UF_{Dura} varies from 1 to 5 depending upon the exposure duration recorded in each record of the CFED. In the following locations, we present UF-specific guidelines for assigning particular UF values in each CFED record:

- UF_{CC}: Table 3-4
- UF_{Inter}: Table 3-8
- UF_{Intra}: Table 3-12
- UF_{Dura}: Table 3-13
- UF_{Conc}: Table 3-14

We applied our UF guidelines to assign a numeric value for all of these UFs to compute CEC SV point estimates in each record of the CFED. Separate sets of UFs were applied to derive the various types of SVs (Table 3-2). Cumulative UF values ($UF_{\prod}$) were computed as the product of UFs associated with several sources of uncertainty (see Section 3.8). The $UF_{\prod}$ was used to adjust a CEC effect concentration (NOAEC or LOAEC) into a conservative estimate of Effect Concentration in a real aquatic system. These adjusted Effect Concentrations are SV point estimates (Figure 2-1; also see Figure 4-2).

Two general types of SVs were derived using the final UFs presented in this chapter. The SV_{HIGH} values are CEC concentrations in surface fresh water above which there is an expectation of adverse effects occurring in freshwater fish, while the SV_{LOW} is a CEC concentration in water below which effects are not expected. The UFs used to derive SV_{HIGH} point estimates ($UF_{\prod\text{-}High}$) were: Chemical Complexity, Inter-species Sensitivity, Intra-Species sensitivity, and Exposure Duration. The derivation of SV_{LOW} point estimates ($UF_{\prod\text{-}Low}$) also incorporated the Effect Concentration UF (UF_{Conc}). Screening value point estimates are obtained by dividing the appropriate Effect Concentrations by cumulative UF values (Figures 1-2 and 2-1; also see Section 4.3.2):

$$SV_{HIGH} = LOAEC / UF_{\prod\text{-}High}$$

$$SV_{LOW} = NOAEC \text{ (or, unbounded LOAEC)} / UF_{\prod\text{-}Low}$$

Specific numeric UF values assigned to compute each SV point estimate are presented in Attachments 4-2A, 4-2B, 4-2C and 4-2D, respectively, for population-relevant SV_{HIGH}, population-relevant SV_{LOW}, comprehensive SV_{HIGH} and comprehensive SV_{LOW} values.

3.1.4 Common Aspects of Empirical UF Derivation

Sufficient information was located from controlled laboratory studies to derive *empirically-based* CEC UF values for Chemical Complexity, Inter-species Sensitivity, and Intra-species Sensitivity. Sections 3.2, 3.3, and 3.4, respectively, describe these UFs in detail, but their derivations included shared features, and these common aspects are discussed in this section.

For each of the three empirical UFs, separate sets of UF values were developed that were used to derive "comprehensive" and "population-relevant" SVs for CECs. Derivation of comprehensive SVs utilizes effect concentrations for all adverse effect endpoints reported in the literature, while population-relevant SVs are based only on data concerning population-relevant adverse effect endpoints (see Figure 2-2 and Attachment 2-1 for explanation of the population-relevance concept). This has resulted in several categories of empirical UFs (Table 3-2). Distributions of UF point estimates were generated for each category, and final UF values for CEC SV derivation were estimated using specific percentiles of these distributions.

3.1.4.1 Empirical UF Database Contents and Point Estimate Derivation

We developed databases of published information to compute UF point estimates for Chemical Complexity, Inter-species Sensitivity, and Intra-species Sensitivity sources of uncertainty. While UFs are used to derive SV point estimates and the CFED includes final UFs in calculations of SV point estimates, these three empirical UF databases are distinct from the CFED. Their purpose was to document the data and calculations for empirical UF point estimates that we used to derive final empirical UF values.

Empirical UF database records were comprised of exposure concentrations (and other study design data) and effect magnitudes from two parallel assays reported in a single published study. The study designs of the paired assays differed principally with respect to a single comparison factor[10]. For the Chemical Complexity UFs, the comparison factor was type of chemical exposure, where one of the paired assays tested one CEC, while the other assay tested that same CEC in a mixture. For the Inter-species Sensitivity UF, paired assays differed only in the fish species tested. Derivation of Intra-species Sensitivity UFs utilized information in paired assays that tested

[10]Comparison factors: Chemical Complexity - single-CEC versus mixture exposure; Inter-species Sensitivity - fish species; Intra-species Sensitivity – life stage or sex.

the same fish species and CEC, but differed in the tested life stage or sex.

Response magnitudes in treatment and control groups were recorded as mean responses (or median, if means were not reported). These values were obtained from tabulated summaries or estimated by visual inspection of graphs provided in the publications. For the Inter-species and Intra-species Sensitivity UFs, effect magnitude was adjusted to reflect percent difference from a negative control. Adjustment of effect magnitude relative to the negative control was necessary because the different comparison groups (e.g., fathead minnows versus bluegill) had separate negative control groups that typically had different mean values. For example, the magnitude of mean growth metrics may differ between negative control groups for fathead minnows and bluegill, or between male minnow controls and female minnow controls. Where a solvent vehicle was used to enhance solubility of the subject CEC, the vehicle control was the preferred control group. Otherwise, the water negative control was used.

Percent difference from control was computed as:

| [(response in treatment group) – (response in control group)] / (response in control group) | * 100%

No adjustment of effect magnitude relative to control was necessary for the Chemical Complexity UF, because both the single-chemical and mixture assays reported in the same publication used the same negative control group.

For a hypothetical example, suppose the response variable was number of eggs produced per female in a pair of parallel reproductive toxicity assays in two different species, reported in one publication as a single integrated study. Suppose that for Species A, the mean responses in the treatment group and negative control group were 100 eggs/female and 1000 eggs/female, respectively, and 50 eggs/female and 2000 eggs/female for Species B. Then the effect magnitudes as percent difference from control would be:

Effect Magnitude for Species A =
[| (100 – 1000) | / 1000] *100% = 90%
Effect Magnitude for Species B =
[| (50 – 2000) | / 2000] * 100% = 97.5%

For the Inter- and Intra-species Sensitivity UFs, UF point estimates were computed by comparing the effect per unit concentration (EPUC) at the LOAEC between the two parallel assays, where exposure and effect concentrations in both assays were reported in the same units. For the Chemical Complexity UF, the EPUC in the highest exposure groups of the single-CEC and mixture assays were computed. Continuing the Inter-Species Sensitivity example above, suppose the LOAEC for Species A was 10 ug/L and the LOAEC for Species B was 0.5 ug/L. Then the EPUC at the LOAEC for Species A would be 90% ÷ 10 ug/L = 9, while the EPUC at the LOAEC for Species B would be 97.5% ÷ 0.5 ug/L = 195. The units for each EPUC are %-L/ug.

The EPUC metrics for the paired assays were computed in each empirical UF database record. Finally, a UF point estimate was computed in each database record as the ratio of the EPUCs from the paired assays. Extending the hypothetical example above, the point estimate for Inter-species UF would be:

Inter-species Sensitivity UF point estimate =
195%-L/ug ÷ 9%-L/ug = 21.7

Since units of EPUCs derived from a given study are identical, each UF point estimate is a unitless quantity. Databases of UF point estimates for Chemical Complexity (UF_{CC}), Inter-species Sensitivity (UF_{Inter}) and Intra-Species Sensitivity (UF_{Intra}) are presented in Attachments 3-2, 3-3 and 3-5, respectively.

For a given effect endpoint it was not known, *a priori*, which tested class would be more sensitive to CEC exposure. But, for the purpose of deriving the UF point estimates, the question is, simply, by how much do the two assays differ? So, the greater EPUC value was always placed in the numerator, regardless which comparison class it is associated with, ensuring that all UF point estimates are ≥ 1. This manner of calculating UF point estimates accommodates the fact that effect magnitude may be positively or negatively related to adverse effect severity, depending upon the effect endpoint. For example, in a reproductive assay, increased embryo mortality corresponds with increased severity of effect (positive relation), whereas, declining number of eggs produced per female also corresponds with increasing severity (negative relation).

The distribution of comprehensive UF point estimates from one of the empirical UF databases used all of the UF point estimates for all effect endpoints. The population-relevant UF point estimate distribution included only UF point estimates associated with population-relevant effect endpoints (see Figure 2-2 and Attachment 2-1 for guidelines on assigning population-relevance to effect endpoints).

3.1.4.2 Final Empirical UF Values as Distribution Percentiles.

The purpose of deriving UF values for multiple sources of uncertainty is to apply them in deriving SVs. For each CEC, paired mean SV_{HIGH} and SV_{LOW} values were derived. The first step in developing the Mean SVs is to develop SV point estimate distributions (see Chapter 4). Uncertainty factors are applied in the denominator of SV point estimate calculations (refer to equations in Section 4.3.2).

Final empirical UF values were obtained as specific percentiles of the UF point estimate distributions. Since the UF values are in the denominator of the SV calculations, higher percentiles of a given UF point estimate distribution would result in lower SV_{LOW} point estimates (i.e., more protective). The smaller the SV_{LOW} value, the greater our confidence that there is no hazard at environmental concentrations below the SV_{LOW}. Hence, the 75th percentile of empirical UF point estimates was selected for computing SV_{LOW} values. Conversely, using a somewhat lower percentile from UF point estimate distributions to calculate SV_{HIGH} point estimates will increase confidence in those values (i.e., will produce higher SV_{HIGH} values). The greater the SV_{HIGH} value, the greater our confidence in assuming that hazardous impacts occur at environmental concentrations exceeding the SV_{HIGH}. Hence, the 25th percentile of the UF point estimate distribution was used to calculate SV_{HIGH} values.

Since neither the mean SV_{HIGH} nor the SV_{LOW} is intended to be an absolute fish toxicity threshold, the use of extreme UF values was not considered. Extremely low UF values may result in excessively high SV_{HIGH} values that are rarely exceeded by measured environmental concentrations. Likewise, extremely high UF values may result in excessively low SV_{LOW} values that are lower than any measured environmental concentrations. Neither of these situations would serve the principal purpose of the CEC SVs, which is pragmatic applicability – such as ranking sampling sites, CECs, and sampling events over time, with respect to potential impacts in fish (see Chapter 4) to inform resource management actions.

Statistical Analysis Software (SAS v9.3 for Windows) PROC UNIVARIATE was used to compute percentiles of point estimate distributions. The 75th percentile of empirical UF point estimate distributions was selected as the final UF value to calculate SV_{LOW}. The 25th percentile was used as the final UF value to compute the SV_{HIGH}. Additional justifications for using percentiles from UF point estimate distributions rather than extreme values include:

- to acknowledge the possibility of UF database errors (such as transcription or graph interpretation error) in records that report UF values in the distribution tail, and

- to increase representativeness of the selected UF values for the whole UF point estimate distribution, rather than representing a specific endpoint in a single species in an individual study that falls in the UF distribution tail.

3.1.4.3 Publication Inclusion/Exclusion Criteria

This section describes quality assurance guidelines related to data that were included in the empirical UF databases, which were used to develop final UF values for the Chemical Complexity, Inter-species Sensitivity, and Intra-species Sensitivity sources of uncertainty. Criteria for lab studies included in the empirical UF databases were developed to minimize the effect of response variability - from sources other than the comparison factor - on UF point estimates. Appropriate published studies were initially identified using the National Library of Medicine TOXLINE database (NLM 2016), USEPA ECOTOX database (USEPA 2016c), Google Scholar search engine, and the literature cited sections in literature reviews and primary literature.

Publication inclusion/exclusion criteria that were common across the three empirical UF databases were:

- *Receptor Groups:* Fish species that live at least part of their life cycle as facultative or obligate residents of freshwater or brackish habitats were included.
- *Study Design:* Only experiments that included an negative control group (vehicle and/or water, as appropriate) were considered.
- *Exposure Duration:* Only studies that exposed fish to CECs for subchronic (7 to 28 days) or chronic (>28 days) exposure durations were included, except where the life stage (or effect endpoint) necessitates considering a shorter duration. Rationale for the duration categories is provided in Section 3.5 – Exposure Duration.
- *Exposure Duration:*
  (a) Aqueous exposure to CECs[11]
  (b) Only in vivo studies are included.
- *Effect Concentration and Magnitude:* Only effect concentrations (LOAEC/LOEC and NOAEC/NOEC) identified in lab experiments were used; no mesocosm data or modeled effect levels were included. Measured concentrations were preferred, but nominal concentrations were accepted if measured concentrations were not reported (see Section 3.6). Where effect endpoint responses are reported only graphically, and graphs were used to estimate effect magnitude by visual inspection, both the exposure concentration and response must be graphed in unit scale (i.e., not log-scale or any other transformation). Both LOAEC (adverse effect endpoints) and LOEC (other effect endpoints) values were included in the UF point estimate calculations, in order to maximize the spread of the empirical UF

[11] Here we are using the term "aqueous exposure" to indicate that the CEC was introduced to the experimental system by dissolving in the exposure water and exposure levels were defined in the study as different concentrations in water, rather than different concentrations in food. While aqueous exposure may imply principally direct update via the gills and integument, we acknowledge that additional routes of exposure likely incidentally include ingestion of CECs in water or ingestion of CECs adhered to food in longer studies that include feeding the fish.

point estimate distributions.

- *Effect Categories and Effect Endpoints:* Only effect endpoints that fell within categories described in Attachment 2-1 were entered into the database. From a given publication, only one record for each unique effect endpoint was entered into the database for each comparison pair. Since multiple endpoints may be evaluated in a study, several comparison pairs may be included from a single publication. For example, a single publication may yield two database records in the Chemical Complexity database for a single endpoint, if that endpoint is measured in two separate single-CEC assays as well as the binary mixture assay of the two CECs. Both adverse and non-adverse effect endpoints were included to develop empirical UF values, in order to maximize the spread of the distribution of UF values.
- *Publication Type:* With few exceptions, only primary publications in peer-reviewed journals were included; any exceptions were noted in the databases.
- *Publication Language:* English, only.
- *Publication Date:* The current version of the databases includes all literature identified in bibliographic searches conducted through July, 2016.

Comparisons *across* publications were not included in order to minimize extraneous and unknowable sources of error, such as may exist between laboratories and research teams, or between assays conducted at different times.

3.1.5 Chapter Organization

The next three sections in this chapter (Sections 3.2 to 3.4) provide details on the derivation, values, and application of empirical UFs for Chemical Complexity, Inter-species Sensitivity, and Intra-species Sensitivity. Sections 3.5 through 3.7 provide application rules and numeric values for non-empirical UFs - Exposure Duration, Effect Concentration, and Database Adequacy – which were selected using scientific judgement based on literature reviews. Cumulative uncertainty - the aggregation of different UFs to derive SV point estimates - is discussed in Section 3.8. Finally, Section 3.9 introduces the concept of the modifying factor, which was not used to derive SVs, but may be applied at practitioners' discretion to adjust SVs on a case-by-case basis to account for uncertainties not otherwise addressed in this document.

Table 3-1. Ranges of uncertainty factors (unitless) for various sources of uncertainty as reported in the literature - for legacy contaminants in EHA applications or in regulatory documents.

Source of Uncertainty	Range of Uncertainty Factor Values for Legacy Contaminants		Description	Information Source
	In Applied EHAs	In Reviews or Regulatory Documents		
Effect Concentration	2 to 10	5 to 55	Extrapolation from unbounded LOAEC to corresponding NOAEC for the same chemical and endpoint, in the same species and life stage	Duke and Taggart 2000
Effect Severity[12]	10 to 300	50 to 500	Extrapolation from observed frank effect level (e.g., mortality, severe lesions) to more subtle individual effect level that may have an indirect effect on populations of the same species exposed for the same duration (e.g., energetic stress, behavioral alterations, suppressed immune system)	Duke and Taggart 2000
		100 to 1000		Zeeman 1995
		1 to 1000[13]		Kenaga 1982
Exposure Duration	1 to 10	2 to 40	Extrapolation of NOAEC after acute or subchronic exposures to corresponding NOAEC after chronic exposure	Duke and Taggart 2000
		10		Zeeman 1995
		25.6[14]		Slooff et al. 1986
Inter-species sensitivity[15,16]	1 to 20	1 to 1000	Extrapolation of NOAEC from the species tested in the laboratory to potentially more sensitive or vulnerable resident species in the location being screened; usually assumes both lab and field species are broadly related taxonomically (e.g., within the same phylum)	Duke and Taggart 2000
		1 to 10		Chapman et al. 1998
		3 to 54[17]		Slooff et al 1986
		6 to 26[18]		Calabrese and Baldwin 1995
Intra-species sensitivity	1	1 to 10	Extrapolation of NOAEC for a specific endpoint in individuals exposed under laboratory conditions to the most sensitive endpoint in the most vulnerable individuals in the same species (e.g., early life stages)	Duke and Taggart 2000
		1 to 10		Chapman et al. 1998
Database Adequacy		1 to 100	Modeled versus measured effect levels; number of available studies; number of relevant species tested; breadth of endpoints evaluated	Chapman et al. 1998
Multiple Stressors	*(this may implicitly be included in one or more of the above UFs)*		Extrapolation from chemical exposure under relatively physiologically neutral laboratory conditions to field conditions in which receptors are continuously exposed to multiple environmental stressors, in addition to the chemical exposure	No reviews located
Chemical Complexity	*(this may implicitly be included in one or more of the above UFs)*		Extrapolation from single-chemical exposure in the laboratory to environmental exposure to a continuously changing chemical mixture that includes the chemical of interest	No reviews located

[12]The UF for effect severity may implicitly include adjustment for exposure duration (e.g., extrapolation from acute LC50 to chronic NOAEC) and data adequacy (e.g., only one QSAR-modeled acute LC50 value available, versus several measured LC50s in multiple species).

[13]98.6% of all acute-chronic ratios (ACRs) (LC50/MATC) in fish, and 96% of fathead minnow ACRs, among 135 total ACRs reviewed by Kenaga (1982) fell between 1 and 999.

[14]Based on 95% upper prediction interval from a linear regression of chronic on acute effect levels for 164 paired values for the same species, representing 11 taxonomic groups including microorganisms, algae, aquatic invertebrates, aquatic and semi-aquatic vertebrates, etc.

[15]The magnitude of UF for inter-specific extrapolation varies greatly with source of the recommended value and the taxonomic distance between lab and field species of interest (order>class>family>genus>species).

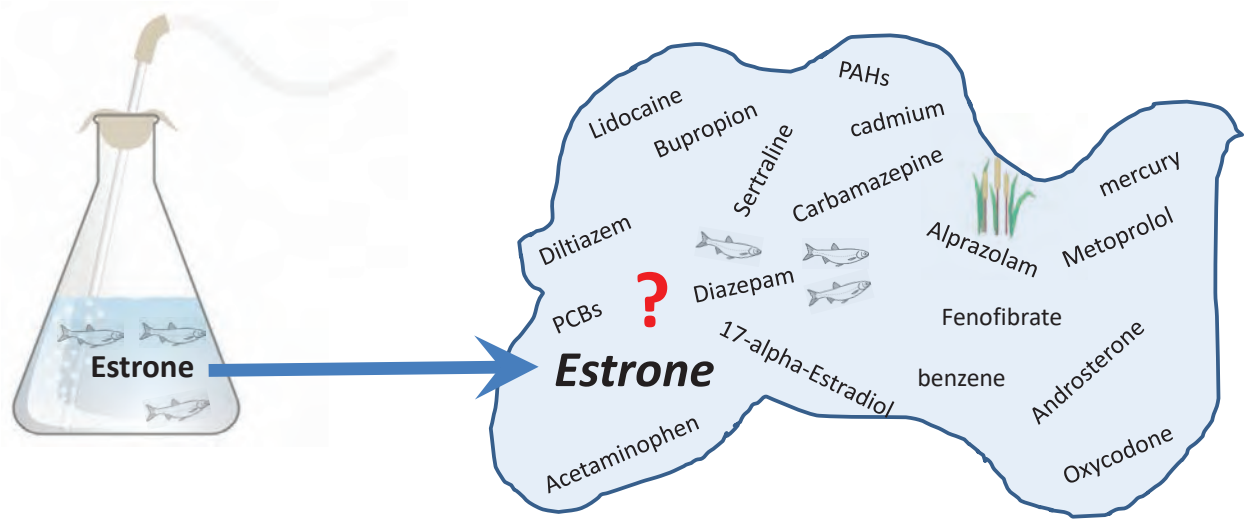
[16]An alternative to applying an uncertainty factor for inter-species sensitivity is the development of a "hazardous concentration" (HCp), which represents a water concentration that adversely affects a certain percentage (p) of species in a community; typically, these are derived only if a chemical has at least a minimal number of relevant effect levels reported in the literature.

[17]Range reported for fish, based on literature review.

[18]Based on acute fish toxicity (LC50) data from the literature, summarized by the authors who obtained their information primarily from Barnthouse et al. (1990). These values are mean weighted upper 95% limit on the upper 95% prediction interval from regression models applied to Cartesian points representing paired LC50 values between two fish species tested in the same assay; N is the total number of fish species pairs tested, across all chemicals in their database. There is a range of mean values because the authors performed the same regression analysis for paired species at four different levels of phylogenetic distance.

Table 3-2. Types of empirical uncertainty factors (UFs) for deriving contaminant of emerging concern (CEC) screening values (SVs) for water exposures in fish. Chemical Complexity, Inter-species and Intra-species UF derivations are described in detail in Sections 3.2, 3.3, and 3.4, respectively.

UF Usage		**Type of Empirical Uncertainty Factor (UF)**		
Effect Endpoint Inclusiveness	**UF Application: Type of SV Derived**	**Chemical Complexity**	**Inter-Species**	**Intra-Species**
Comprehensive	**SV_{HIGH}**	Comprehensive type UF_{CC}-High	Comprehensive type UF_{INTER}-High	Comprehensive type UF_{INTRA}-High
	SV_{LOW}	Comprehensive type UF_{CC}-Low	Comprehensive type UF_{INTER}-Low	Comprehensive type UF_{INTRA}-Low
Population-relevant	**SV_{HIGH}**	Population-relevant UF_{CC}-High	Population-relevant UF_{INTER}-High	Population-relevant UF_{INTRA}-High
	SV_{LOW}	Population-relevant UF_{CC}-Low	Population-relevant UF_{INTER}-Low	Population-relevant UF_{INTRA}-Low



3.2 Chemical Complexity

3.2.1 Purpose

The purpose of the Chemical Complexity UF (UFCC) is to quantify that portion of total extrapolation uncertainty attributable to differences in chemical complexity, where single-CEC lab study LOAECs or NOAECs are adjusted to estimate corresponding effect concentrations for environmental mixture exposures in freshwater fish. It is used to extrapolate single-CEC effect concentrations (LOAECs or NOAECs) in water that were identified in a controlled laboratory study to an exposure scenario involving the same CEC in a mixture.

3.2.2 Background

In 2015, the American Chemical Society's Chemical Abstract Service (CAS) assigned its 100 millionth CAS Registry Number (CASRN) to a chemical substance (CAS 2015). That number continues to grow. The CASRNs are numeric chemical identifiers, which are assigned to both synthetic and naturally occurring chemicals. While some chemicals have multiple CASRNs, the vast majority are uniquely identified by a single CASRN. Among these millions of known substances, researchers consistently cite the number of commercially available synthetic chemicals that are produced on an industrial scale at approximately 100,000 (e.g., Brown and Wania 2008, Snyder et al. 2000, UNEP 2014, von der Ohe et al. 2011). Among chemicals in commerce, an estimated 40,000 have been identified as CECs (e.g., Diamond et al. 2011). Hence, it is reasonable to expect complex mixtures of anthropogenic chemicals, including numerous CECs, to be present in aquatic systems with known contaminant sources.

Chemicals in environmental mixtures may interact with each other additively, synergistically, or antagonistically, or they may act independently, to produce a combined effect. In many of the laboratory studies in fish that were used to derive UFCC values, the chemicals in the tested mixtures were selected for common expected biological activity, such as estrogenic chemicals (Brian et al. 2005, Hua et al. 2013, Jukosky et al. 2008, Lin and Janz 2006, McGee et al. 2009, Thorpe et al. 2003), antidepressants (Painter et al. 2009, Schultz et al. 2011), and antimicrobials (Schultz et al. 2012). In other mixture studies that were used to derive UFCC values, component chemicals did not fall neatly into a common biological activity group. Some of these mixtures were expected to be potentially synergistic or additive (Keiter et al. 2012, Wu et al. 2011, Xu et al. 2013), antagonistic (Sun et al. 2009), or to have apparently disparate biological activities among the tested chemicals (Armstrong et al. 2015, Madureira et al. 2012, Zenobio et al. 2014).

While the vast majority of the available literature on laboratory CEC toxicity studies in fish is based on single-chemical exposures, a significant number of CEC mixture studies in fish have been published (Attachment 3-1). A subset of these CEC mixture studies evaluated both mixture toxicity in fish, and the toxicity of individual component CECs. Criteria for inclusion in the dataset used to derive the UFCC values were applied to publications that reported on paired mixture- and single-CEC assays.

3.2.3 UFcc Database - Data Inclusion Criteria

A database was developed specifically for the purpose of deriving and documenting UFCC point estimates (Attachment 3-2). The UFCC was quantified using published studies in fish that tested for both single-CEC effects and mixture effects of the same CEC in water, for the same endpoints. General inclusion criteria that are common across all three empirical UFs are provided in Section 3.1.4.

Inclusion criteria specific to the UFCC were the following:

- *Chemical Complexity Classes:* A single publication must report results from two parallel assays that evaluated for effects from

exposure to the subject CEC - a single-CEC assay and in a mixture assay that includes the subject CEC.

- *Chemical Scope:* (a) Subject CECs were not limited to those for which SVs were derived; (b) no legacy contaminant UFCC values were derived, however, legacy contaminants may be part of a tested chemical mixture that included at least one subject CEC; (c) the number of mixture constituents was not limited.
- *Effect Concentration:*
  - o Statistically significant effects were reported in the highest exposure group, either in the single-CEC experiment, the mixture experiment, or both.
  - o Effect magnitude at both control and highest exposure groups are reported in both experiments in either tabular or graphic format.
  - o Both LOAEC (adverse endpoints) and LOEC (non-adverse endpoints) effect concentrations were included in the UF point estimate calculations, in order to maximize the spread of the UF point estimate distribution

3.2.4 UFCC Database Structure and Contents

Database fields are organized into the following groups: Study Attributes, Comparison Information, Computations, and Supporting Information. The following list identifies the fields in the database that are included in each group. Attachment 3-2 provides information on a subset of the fields in the electronic database related to UFCC derivation. Groups and fields are presented in the database in this order:

Study Attributes

- CEC Category
- CEC
- Effect Category
- Effect Endpoint
- Relation of Endpoint Magnitude with Degree of Hazard (pos/neg)
- Population-relevant Endpoint (Y/N)
- Species

Comparison Information

- High Exposure Group CEC Concentration (ppb) for Single CEC Assay
- Single CEC Assay: Signif Diff from Control? (Y/N)
- High Exposure Group Effect Magnitude for CEC in Single Chemical Assay
- Single CEC Assay Response Data Presentation (G ="Graph" or T="Table or Text")
- High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay
- Mixture CEC Assay: Signif Diff from Control? (Y/N)
- High Exposure Group Effect Magnitude for CEC in Mixture Assay
- Mixture CEC Assay Response Data Presentation (G ="Graph" or T="Table or Text")

Computations

- Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)
- Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)
- UFCC Point Estimate - Ratio of EPUCs (higher/lower)

Supporting Information

- Notes
- Publication Reference

The UFCC database records are uniquely differentiated based on the following information: Publication Reference, CEC, Effect Endpoint, Species, and sometimes fish sex (as recorded in the Notes field). The database consists of 171 records extracted from 14 peer-reviewed, published papers. Each record conforms to the data inclusion criteria (Sections 3.1.4 and 3.2.3).

Represented in the database are:

- 18 CECs tested as single chemicals and in a mixture in the same study (Table 3-3);
- 11 CEC Categories (Table 3-3);
- 4 freshwater or brackish water fish species representing various niches;
- 9 Effect Categories.

3.2.5 UFCC Point Estimate Derivation

Aspects of UF derivation that are shared among all three empirical UFs are presented in Section 3.1.4. One UFCC point estimate was calculated in each record of the UFCC database. Exposure and effect data from the single-CEC highest exposure group and the corresponding mixture highest exposure group were used to calculate UFCC point estimates. Since both assays utilized exposure groups with the same species/sex/life stage composition, comparisons between the highest exposure groups were expected to yield the greatest differences in effect magnitude between the paired assays (for a given effect endpoint), hence the greatest spread in the distribution of UFCC point estimates. A wide spread in the UFCC point estimates distribution was assumed to result in conservative UFCC estimates for the purpose of deriving SVs.

In most UFCC database records, both the measured CEC concentration and effect magnitude differ between the high exposure groups in the single-CEC and mixture tests. In some cases the highest exposure levels in the single-CEC and mixture assays have different measured concentrations, yet they result in essentially the same effect magnitude, indicating greater potency of the subject CEC in the group with

the lower maximum exposure concentration. Likewise, different effect magnitudes in the single- versus mixture-exposed group may result from exposure to essentially the same CEC concentration, indicating higher potency in the group showing the greater adverse effect. Relative potency of the CEC was represented in both the single-CEC assay and the mixture assay by using the ratio of the effect magnitude to exposure concentration – the effect-per-unit-concentration (EPUC) - in the highest exposure groups.

Unlike in the derivations of empirical Inter-species and Intra-species UFs, calculation of UFCC point estimates did not involve adjusting effect magnitude to percent difference from the negative control. This is because both the single-CEC and mixture assays used the same negative control group, so the value of any UF estimate would not be affected by adjusting effect magnitudes.

In each UFCC database record, the following computations were conducted:

- The EPUC in the high-concentration group for the single-CEC assay was computed as:

  $EPUC_{SINGLE}$ =
  Effect magnitude $_{SINGLE}$ / $[CEC]_{SINGLE}$.

- The EPUC in the high-concentration group for the mixture assay was computed as:

  $EPUC_{MIXTURE}$ =
  Effect magnitude $_{MIXTURE}$ / $[CEC]_{MIXTURE}$.

  where,
  $[CEC]_{SINGLE}$ and $[CEC]_{MIXTURE}$ are the concentrations of the same CEC in the highest exposure group in each assay

- One UFCC point estimate was computed in each database record as:

  UFCC = EPUC1 / EPUC2.

  where,
  EPUC1 = the greater value between $EPUC_{SINGLE}$ and $EPUC_{MIXTURE}$

  EPUC2 = the lesser value between $EPUC_{SINGLE}$ and $EPUC_{MIXTURE}$

3.2.6 UFCC Point Estimates and Final Values

All UFCC point estimates are based on comparisons of effective potency between an assay of a CEC in mixture and the same CEC tested singly, with other factors held constant. Two UFCC point estimate distributions were developed. One distribution contains all of the point estimates in the database (Figure 3-1), and was used to obtain "comprehensive type" UFCC values for derivations of comprehensive type SV_{HIGH} and SV_{LOW} values. The second distribution contains comparisons involving only population-relevant endpoints (i.e., behavioral, developmental, growth, reproductive, and survival specified in Attachment 2-1), and was used to obtain "population-relevant" UFCC values (Figure 3-2).

The range of values of both comprehensive and population-relevant UFCC point estimates is 1 to 118.8. No literature values of UFCC for legacy contaminants were located for comparison (Table 3-1).

Specific percentiles of the comprehensive- and population-relevant UFCC point estimate distributions were selected for deriving SV_{HIGH} and SV_{LOW} point estimates (Table 3-4). Rationale for selected percentiles is provided in Section 3.1.4.2: *Final Empirical UF Values as Distribution Percentiles.*

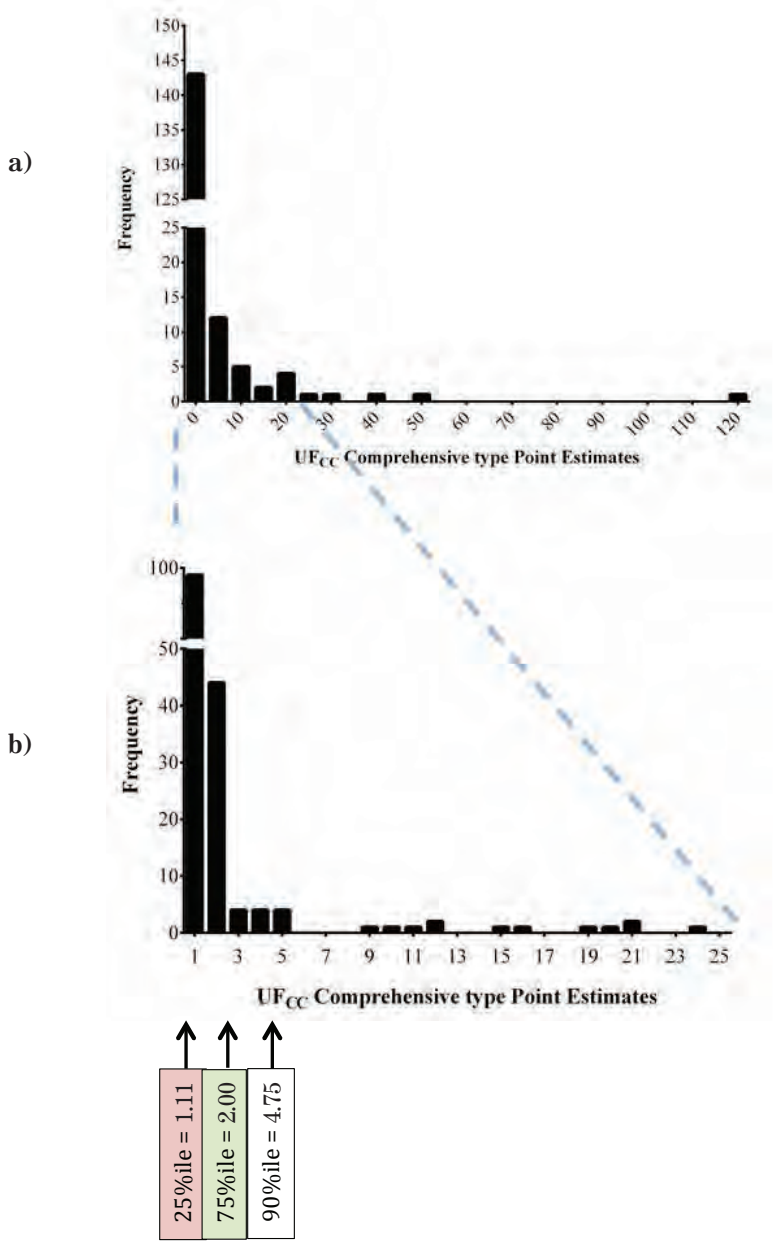


Figure 3-1. Frequency distribution of (a) all and (b) a focused subset of Comprehensive Chemical Complexity UF (UFcc) point estimates derived from data reported in publications that evaluate effects from a given CEC in both a single-CEC assay and contaminant mixture assay, for all adverse effect endpoints. Selected percentiles of the distribution of point estimates are indicated (N=171; Min=1; Max=118.8). The UFcc 25%ile and 75%ile values were used to derive comprehensive type SV$_{HIGH}$ and SV$_{LOW}$ point estimates, respectively. X-axis values are mid-points of intervals.

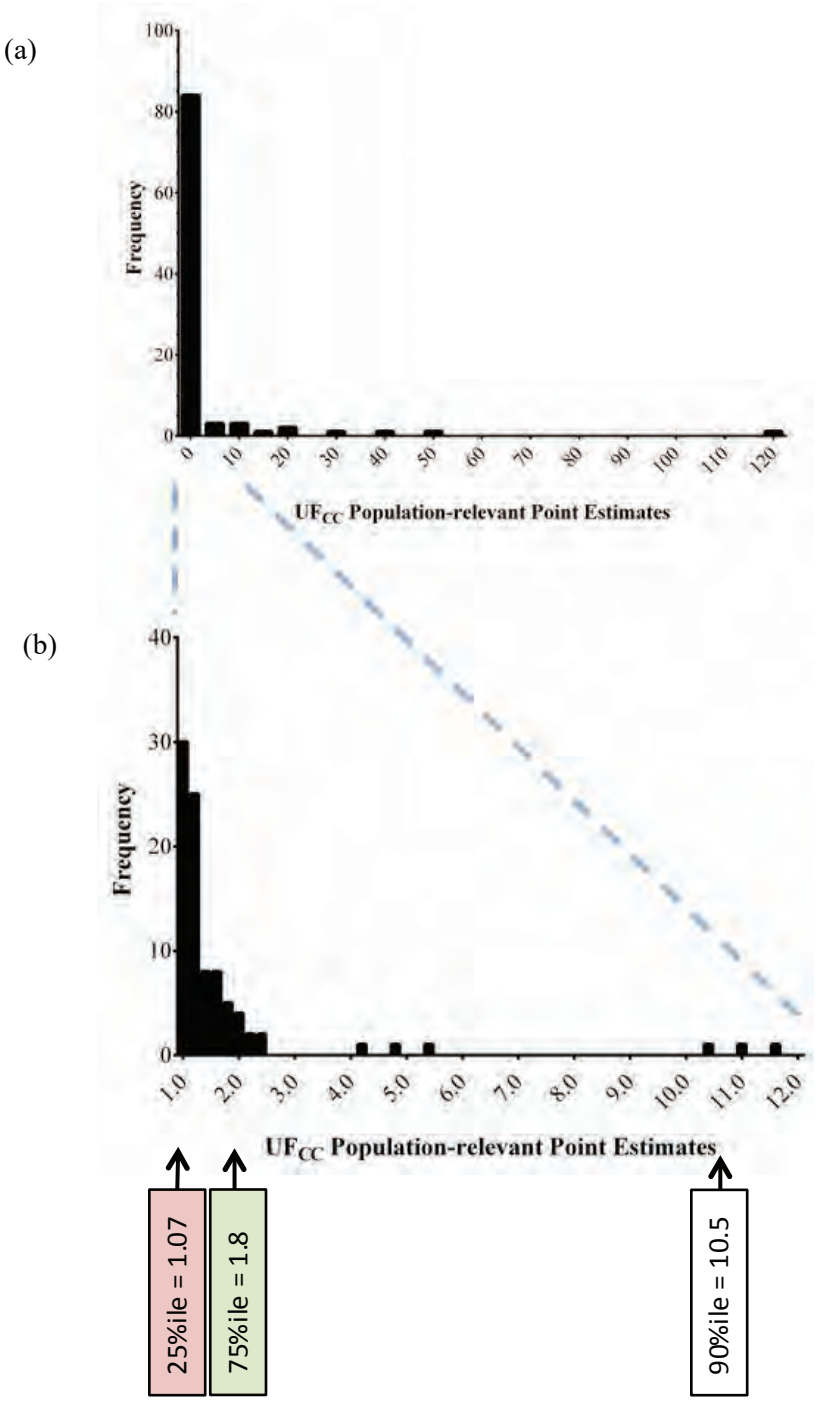


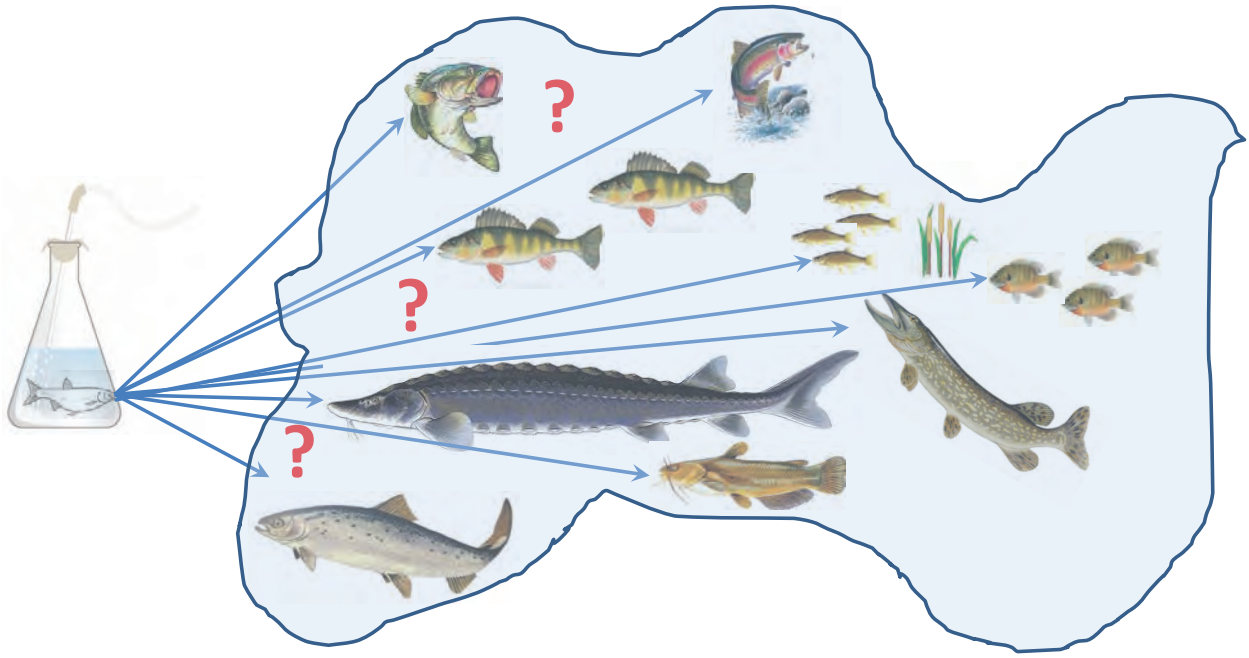
Figure 3-2. Frequency distribution of (a) all and (b) a focused subset of population-relevant Chemical Complexity UF (UFcc) point estimates derived from data reported in publications that evaluate effects from a given CEC in both a single-CEC assay and contaminant mixture assay, for population-relevant adverse effect endpoints. Selected percentiles of the distribution of point estimates are indicated (N=97; Min=1; Max=118.8). The UFcc 25%ile and 75%ile values were used to derive population-relevant SV$_{HIGH}$ and SV$_{LOW}$ point estimates, respectively. X-axis values are mid-points of intervals.

Table 3-3. List of 18 CECs in 11 CEC categories for which laboratory studies were located that test for adverse effects in fish after both single-CEC and mixture exposures in water.

CEC Category	CEC
Alkylphenol	Nonylphenol
Flame Retardant / Surfactant	Perfluorooctane sulfonate
Hormone	17a-ethinylestradiol (EE2)
	17B-estradiol (E2)
	Estrone (E1)
Insect Repellent	DEET
Personal Care – antimicrobial	Triclosan
	Triclocarban
Pharmaceutical – antibiotic	Sulfamethoxazole
	Trimethoprim
Pharmaceutical – anti-cholesterol	Fenofibric Acid
Pharmaceutical – anticonvulsant	Carbamazepine
Pharmaceutical – antidepressant	Bupropion
	Fluoxetine
	Sertraline
	Venlafaxine
Pharmaceutical – beta blocker	Propranolol Hydrochloride
Plasticizer	Bisphenol A

Table 3-4. Final UF_{CC} values (unitless) are based on percentiles of the UF_{CC} point estimate distribution, and are used to derive water screening values to characterize CEC hazards to freshwater fish. The UF_{CC} 25%ile and 75%ile values were used to derive SV_{HIGH} and SV_{LOW} point estimates, respectively.

Effect Endpoint Inclusiveness	SV Application	UF_{CC} in SV Derivation	Effect Categories	N	Percentiles in UF_{CC} Point Estimate Distribution	**Final UF_{CC} Values (unitless)**
Population-relevant	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse Population effects ARE NOT expected in wild fish	Behavioral Developmental Growth Reproductive Survival	97	99%ile = 118 95%ile = 21.4 90%ile = 10.5 75%ile = 1.80 50%ile = 1.30 25%ile = 1.07 10%ile = 1.03 5%ile = 1.01 1%ile = 1.00	**1.8**
Population-relevant	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse Population effects ARE expected in wild fish				**1.1**
Comprehensive	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse effects in Individual fish ARE NOT expected in the wild	All Effect Categories	171	99%ile = 50 95%ile = 18.9 90%ile = 4.75 75%ile = 2.00 50%ile = 1.32 25%ile = 1.11 10%ile =1.03 5%ile = 1.02 1%ile = 1.00	**2.0**
Comprehensive	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse effects in Individual fish ARE expected in the wild				**1.1**



3.3 Inter-Species Sensitivity

3.3.1 Purpose

The purpose of the Inter-Species Sensitivity UF is to quantify that portion of total extrapolation uncertainty attributable to differences in fish species sensitivity. It is used to extrapolate exposure-effect relationships (expressed as a LOAEC/LOEC or NOAEC/NOEC) from a controlled laboratory study that tested for effects in a single species to an estimated effect concentration in a receptor species or group of species that are more sensitive to the subject CEC.

3.3.2 Background

There are over 15,000 species of freshwater fish worldwide (IUCN 2016) that exhibit great differences in morphology, life history and ecological niche, and inhabit a diverse array of habitats. Among these, at least 160 fish species are resident in the Great Lakes Basin (Hubbs and Lagler 2004). Inadequately representing this natural variety are perhaps only several dozen obligate or facultative freshwater fish species that have ever been tested in controlled ecotoxicological assays, and fewer that have been tested for effects from CEC exposure. Most of the lab species are physically small and short-lived, due to pragmatic considerations such as cost, lab space, life cycle duration, and repeatability, as well as potentially poor survival and reproduction in large-body fish under laboratory conditions. Certain fish species are dominantly represented in the CEC ecotoxicity literature, including the fathead minnow (*Pimephales promelas*), Japanese medaka (*Oryzias latipes*), and zebrafish (*Danio rerio*). For the purpose of determining relative potency among chemical contaminants, the small number of frequently tested species is advantageous because it limits fish species as a source of variation among ecotoxicity tests on different chemicals. However, limited species representation in the ecotoxicity literature is disadvantageous for investigators who wish to estimate relative chemical hazard in a more sensitive – usually unidentified – species assumed to be present in a natural system.

Ecotoxicologists have developed several approaches to the problem of variable species sensitivity in extrapolating lab test results to natural systems. Human health risk assessment guidance provides precedent for the application of an inter-species uncertainty factor to an appropriate effect concentration (e.g., NOAEC/NOEC or LOAEC/LOEC) (USEPA 1989). Ecological risk assessors sometimes use percentiles from species sensitivity distributions (SSDs), which are distributions of unadjusted effect concentrations, either acute or chronic exposure durations, obtained from the literature for relevant species. See Attachment 4-1 for examples of reference values developed as percentiles of SSDs. In addition, empirical regression modeling approaches have been developed to predict an acute effect concentration (LC_{50} or EC_{50}) in an untested species from measured effect concentrations obtained for species tested in laboratory assays (USEPA 2016d).

Our approach to SV development focused on effects after chronic exposures and involved calculation of SV point estimates. Hence, we adjusted each relevant chronic effect concentration in the CFED with UFs (including an Inter-species UF). The rationale and methods for deriving distributions of SV point estimates are provided in Section 4.3.2.
The published literature of laboratory CEC toxicity studies in fish is dominated by single-species exposure studies. The UF_{Inter} is applied because chemical sensitivity in lab species may be different from potential receptor species' sensitivity in a natural system. This UF is intended to account for inter-

species differences in sensitivity and magnitude of *direct* toxic effects. The UF_{Inter} does *not* account for differences among species in susceptibility to *indirect* effects, such as potential cumulative or compensatory population effects in the species of interest due to shifts in aquatic community structure or composition that may result from CEC exposure in multiple fish species over many generations.

3.3.3 UF_{Inter} Database - Data Inclusion Criteria

A database specifically for the purpose of deriving and documenting UF_{Inter} point estimates was developed (Attachment 3-3). The UF_{Inter} was quantified from published laboratory assays. General inclusion criteria that are common across all three empirical UFs are provided in Section 3.1.4.

Inclusion criteria specific to the UF_{Inter} were the following:

- *Inter-Species Sensitivity Classes:* A single publication must report results from two or more parallel assays that evaluate for effects in the same endpoint(s) and same life stage due to CEC exposure, but in different fish species,
- *Chemical Scope:* (a) The subject CECs were *not* limited to those for which SVs were derived. (b) Studies of legacy contaminants were excluded, except where legacy contaminants were part of a mixture that included at least one subject CEC. Both single-CECs and mixtures were represented that were tested in multiple species were included.
- *Effect Concentration and Magnitude:*
    - Both LOAEC (adverse endpoints) and LOEC (non-adverse endpoints) values were included in the UF point estimate calculations, in order to maximize the spread of the UF point estimate distribution
    - A LOAEC/ LOEC must be reported in each of the paired fish species assays for a given effect endpoint
    - Effect magnitudes in the control and LOAEC/ LOEC exposure groups are reported in both species' experiments, in either tabular or graphic format.

3.3.4 UF_{Inter} Database Structure and Contents

Database fields are organized into the following groups: Study Attributes, Comparison Information, Computations, and Supplemental Information. Groups and fields are presented in the database in the following order:

Study Attributes

- CEC Category
- CEC
- Effect Category
- Effect Endpoint
- Population-relevant Endpoint (Y/N)

Comparison Information

- Species 1 – Species Common Name
- Species 1 – LOAEC/LOEC (ug/L)
- Species 1 – LOAEC/LOEC Effect Magnitude
- Species 1 – Control Group Effect Magnitude
- Species 1 – EML1 - Effect Magnitude at LOAEC/LOEC (as % difference from negative control)
- Species 1 - Effect Data Source in Paper (Specific Figure or Table)
- Species 1 Effect Data Presentation (G ="Graph" or T="Table or Text")
- Species 2 – Species Common Name
- Species 2 – LOAEC/LOEC (ug/L)
- Species 2 – LOAEC/LOEC Effect Magnitude
- Species 2 – Control Effect Magnitude
- Species 2 - EML2 - Effect Magnitude at LOAEC/LOEC (as % difference from negative control)
- Species 2 - Effect Data Source in Paper (Specific Figure or Table)
- Species 2 - Effect Data Presentation (G ="Graph" or T="Table or Text")

Computations

- Species 1 – EPUC1 - Effect per unit Conc at LOAEC/LOEC (EML1/LOAEC or LOEC)
- Species 2 – EPUC2 - Effect per unit Conc at LOAEC/LOEC (EML2/LOAEC or LOEC)
- UFI_{Inter} Point Estimate - Ratio of EPUCs (higher/lower)

Supporting Information

- Notes
- Publication Reference

Records in the UF_{Inter} point estimate database are uniquely identified based on the following fields: Publication Reference, CEC, Effect Endpoint, Species, and sometimes fish sex (if recorded in the Notes field). The database consists of 65 records extracted from 15 peer-reviewed, published papers. Each record conforms to the data inclusion criteria (Sections 3.1.4, 3.3.3).

Represented in the UF_{Inter} point estimate database are:

- 17 individual CECs (or mixtures) tested in water exposures in two or more fish species (Table 3-5);
- 8 CEC Categories (Table 3-5);
- 16 freshwater or brackish water fish species representing a variety of niches (Table 3-6; Attachment 3-4);
- 23 unique pairwise species comparisons (pairwise species comparisons were represented in the database between 1 and 8 times) (Table 3-6; Attachment 3-3);
- 7 Effect Categories (Table 3-7).

3.3.5 UF_{Inter} Point Estimate Derivation

Aspects of UF derivation that are shared among all three empirical UFs are presented in Section 3.1.4.

One UF_{Inter} point estimate was calculated in each record of the UF_{Inter} database. Each record in the inter-species sensitivity database represents an endpoint-specific binary comparison of relative sensitivity between two fish species after exposure to CEC. Unlike other studies of the inter-species uncertainty factor (e.g., Calabrese and Baldwin 1994, 1995), this analysis did not stratify observations using higher levels of taxonomic organization (e.g., by genus or family); all of the pairwise comparisons are species to species, regardless of higher taxonomic classifications. An analysis comparable to the Calabrese and Baldwin papers of the influence of phylogenetics on empirical CEC inter-species UF values is beyond the scope of this document. We did not use the USEPA Interspecies Correlation Estimation (ICE) model to estimate effect concentrations in untested species, because we are developing UFs based on effects after chronic exposures to use in deriving chronic aqueous SVs, but ICE utilizes information on acute effects to predict effect concentrations across species (USEPA 2016d).

Our approach built on the work of Calabrese and Baldwin (1994, 1995) by utilizing the following types of information:

- Exposure-effect information focused on CECs (not legacy contaminants),
- Effect concentrations for a diversity of adverse endpoints (not just mortality),
- Chronic exposure assay response data (not acute exposure assays),
- NOAEC/NOEC and LOAEC/LOEC values (rather than ECx or LCx),
- Comparisons between paired assays in different species across different levels of organization (i.e., species-species comparisons across different genera, or across families) rather than only between species within genera.

We used two variables that were reported for each species to quantify inter-species differences in sensitivity for individual effect endpoints: the LOAEC/LOEC, and the magnitude of the response at the LOAEC/LOEC. We calculated UF point estimates for each endpoint for which a LOAEC/LOEC was identified in both tested species. Mean (or median) effect magnitude at the LOAEC/LOECs were obtained for each species from the publication. Effect magnitudes were quantified by effect endpoint as the percent difference in the response at the LOAEC/LOEC from the corresponding negative control response. We represented relative sensitivity of each of the tested species using the effect-per-unit-concentration (EPUC) at the LOAEC/LOEC, which is computed as the ratio of the mean effect magnitude at the LOAEC/LOEC to the LOAEC/LOEC concentration for that species.

This approach differs from that used to derive UF_{CC} point estimates, where the concentrations and effect magnitudes of the highest exposure groups in paired single-CEC and mixture assays were utilized. For UF_{CC} derivations, only one or the other of the highest exposure groups was required to be a LOAEC/LOEC. For UF_{Inter} derivations, the two different species in the paired assays likely have intrinsically different sensitivities to the tested CEC for a given effect endpoint (i.e., different negative control responses), so the LOAEC/LOEC values for each of the two species were required.

In each UF_{Inter} database record, the following computations were conducted:

1) The EPUC in the Species 1 assay was computed as:
   $EPUC_{Species\ 1}$ =
   Mean effect magnitude at LOAEC/LOEC$_{Species\ 1}$ / LOAEC/LOEC$_{Species\ 1}$

2) The EPUC in the Species 2 assay was computed as:
   $EPUC_{Species\ 2}$ =
   Mean effect magnitude at LOAEC/LOEC$_{Species\ 2}$ / LOAEC/LOEC$_{Species\ 2}$

where,

LOAEC/LOEC$_{Species\ 1}$ and LOAEC/LOEC$_{Species\ 2}$ are concentrations of the same CEC associated with responses in the same effect endpoint that are significantly different from the respective control groups.

3) A UF_{Inter} point estimate was computed in each database record as:

$$UF_{Inter} = EPUC_A / EPUC_B.$$

where,

$EPUC_A$ = the greater value between $EPUC_{Species\ 1}$ and $EPUC_{Species\ 2}$

$EPUC_B$ = the lesser value between $EPUC_{Species\ 1}$ and $EPUC_{Species\ 2}$

3.3.6 UF_{Inter} Point Estimates and Final Values

All UF_{Inter} point estimates are based on publications reporting paired assays that compare relative sensitivity in different fish species in the same effect endpoints, with other factors held constant. Two UF_{Inter} point estimate distributions were developed. One distribution contains all of the point estimates in the UF_{Inter} database (Figure 3-3), and was used to obtain "comprehensive type" UF_{Inter} values for derivations of comprehensive type SV_{HIGH} and SV_{LOW} values. The second distribution contains comparisons involving only population-relevant endpoints (i.e., behavioral, developmental, growth, reproductive, and survival) (Figure 3-4), and was used to obtain "population-relevant" UF_{Inter} values.

Specific percentiles of the comprehensive- and population-relevant UF_{Inter} point estimate distributions were selected for deriving SV_{HIGH} and SV_{LOW} point estimates (Table 3-8). Rationale for selecting certain percentiles as final UF values is provided in Section 3.1.4.2: *Final Empirical UF Values as Distribution Percentiles.*

The range of values of comprehensive type UF_{Inter} point estimates is 1 to 353, while population-relevant UF_{Inter} point estimates range from 1 to 35. The UF_{Inter} values that were selected as percentiles of empirical point estimate distributions (Table 3-8) are within the ranges of UF_{Inter} values reported in the literature for legacy contaminants (Table 3-1).

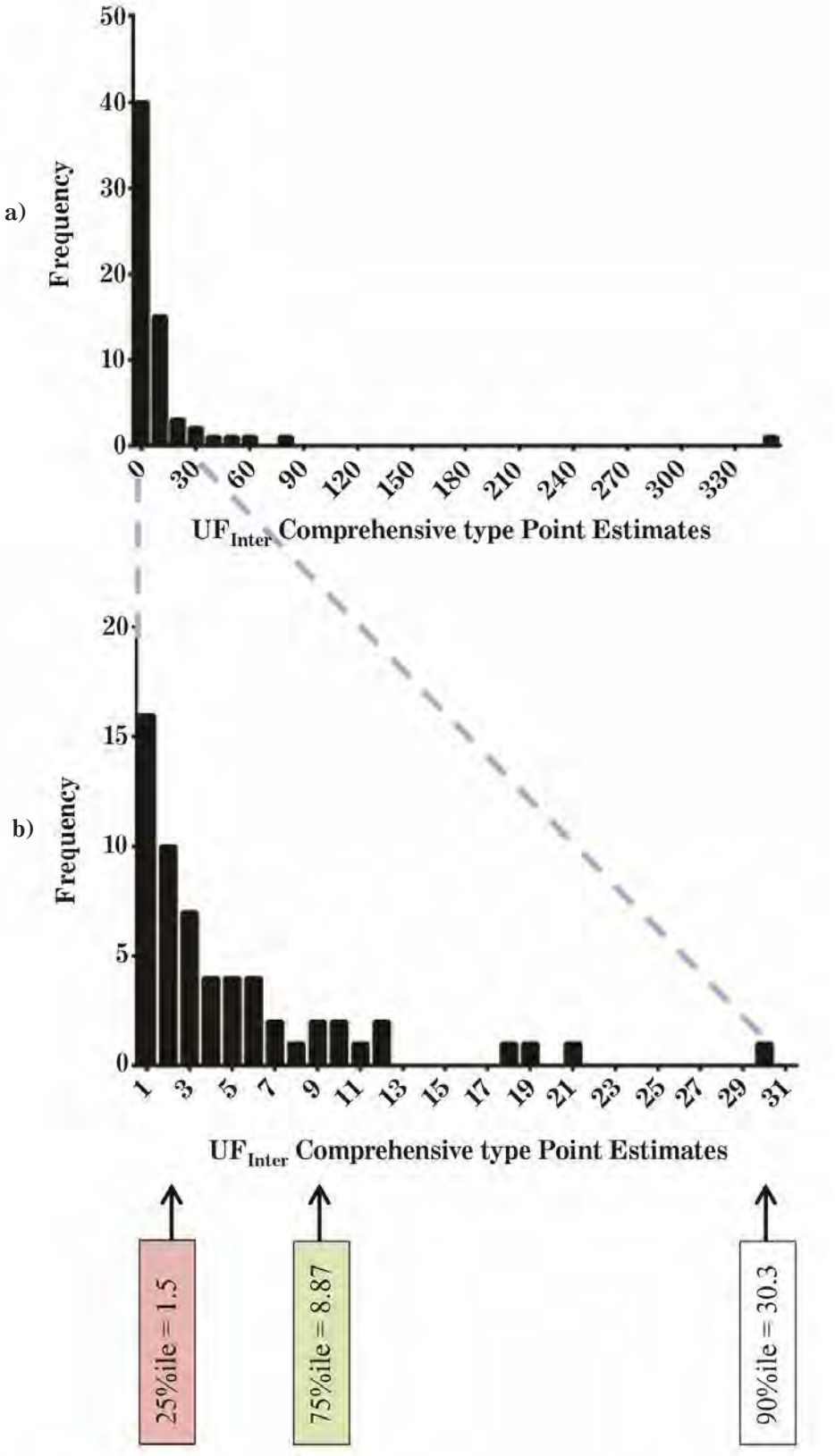


Figure 3-3. Frequency distribution of (a) all and (b) a focused subset of comprehensive type Inter-Species UF (UF_{Inter}) point estimates derived from data reported in publications that evaluate the same effects (all adverse effect endpoints) from exposure to a given CEC in two or more species. Selected percentiles of the distribution of all point estimates are indicated (N=65; min=1; max=353). The UF_{Inter} 25%ile and 75%ile values were used to derive comprehensive SV_{HIGH} and SV_{LOW} point estimates, respectively. X-axis values are mid-points of intervals.

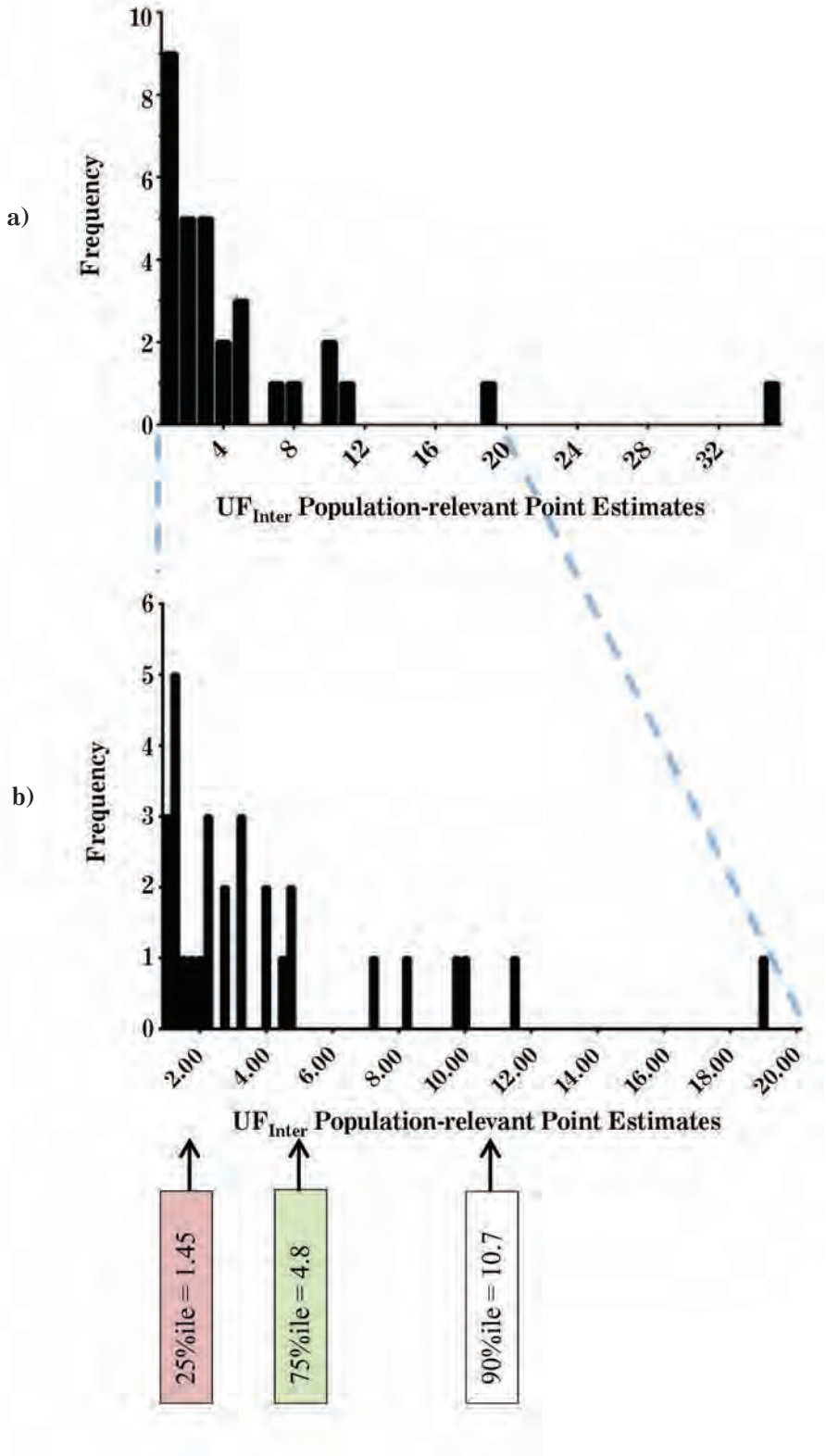


Figure 3-4. Frequency distribution of (a) all and (b) a focused subset of population-relevant Inter-Species UF (UF_{Inter}) point estimates derived from data reported in publications that evaluate the same effects (population-relevant adverse effect endpoints) from exposure to a given CEC in two or more species. Selected percentiles of the distribution of all point estimates are indicated (N=30; min=1; max=35). The UF_{Inter} 25%ile and 75%ile values were used to derive population-relevant SV_{HIGH} and SV_{LOW} point estimates, respectively. X-axis values are mid-points of intervals.

Table 3-5. List of CEC Categories and individual CECs (and CEC mixtures) for which publications of laboratory studies were located that included parallel assays in two or more fish species.

CEC Category	CEC	Number of Database Records
Complex Mixture	Untreated pulp mill effluent	1
	Pulp mill effluent after primary treatment	1
	Pulp mill effluent after secondary treatment	1
Fungicide	Imidazole Ketoconazole	4
	Prochloraz	10
Herbicide	Picloram	2
Hormone	17a-ethinylestradiol (EE2)	9
	17B-estradiol (E2)	3
	Norethindrone	1
	Spironolactone	5
	Testosterone	2
Personal Care – UV filter	Benzophenone-3	1
Pharmaceutical – beta blocker	Propranolol	1
Pharmaceutical – Nonsteroidal Aromatase Inhibitor	Fadrazole	3
Surfactant	Octoxynol 9 (Triton X-100)	7
	Perfluorooctane sulfonate (PFOS)	13
	Sodium dodecyl sulphate (SDS)	1
	TOTAL	65

Table 3-6. Number of database records containing pairwise comparisons of fish species' relative sensitivity to CEC exposure for the same effect endpoint. Each database record provides a single empirical UF_{Inter} point estimate based on a pairwise inter-species comparison of LOAEC values and effect response magnitudes.

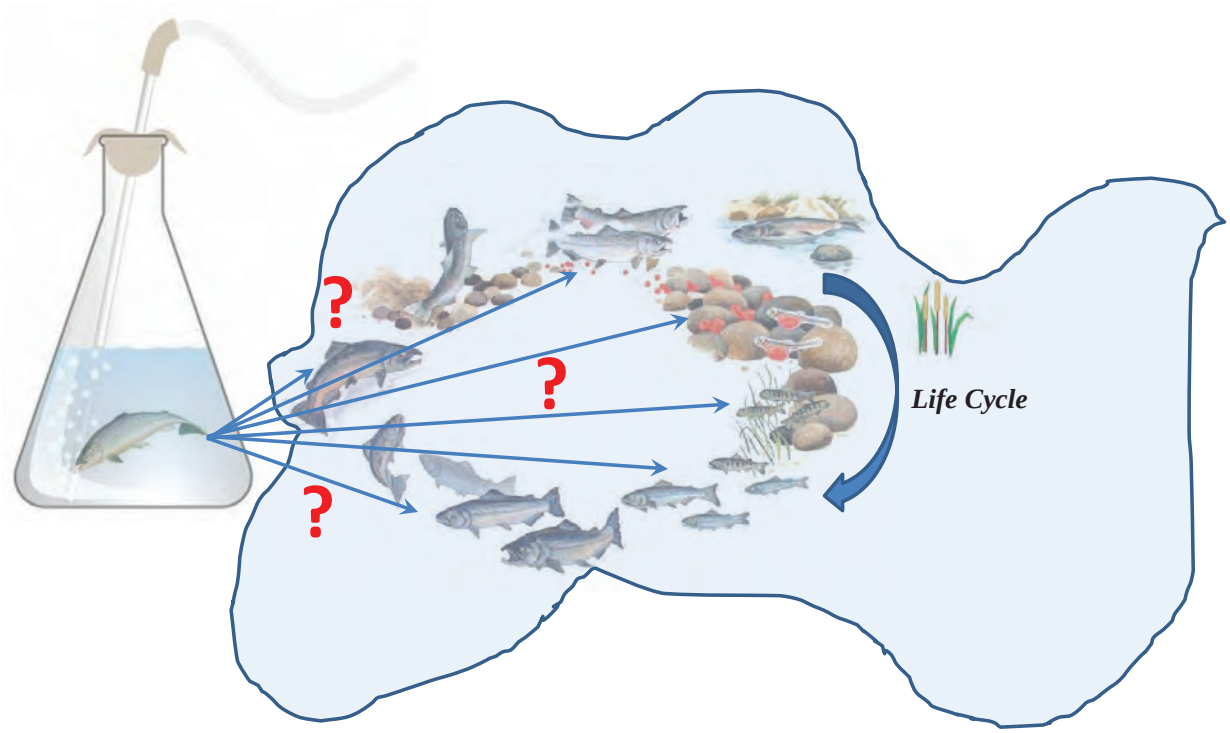
Species 1	Species 2	Number of UF_{Inter} Database Records
Brown Trout	Common Carp	8
Bull Trout	Rainbow Trout	2
Creek Chub	Spottail Shiner	3
Fathead Minnow	Bluegill	1
	Japanese Medaka	8
	Rainbow Trout	6
	Roach	1
	White Sucker	1
	Zebrafish	7
Flagfish	Japanese Medaka	1
Japanese Medaka	Rainbow Trout	7
	Zebrafish	7
Rainbow Trout	Killifish	4
Rio Grande Silvery Minnow	Fathead Minnow	1
Stickleback	Japanese Medaka	1
	Rainbow Trout	1
	Zebrafish	1
White Sucker	Creek Chub	1
	Rainbow Trout	2
	Spottail Shiner	1
Zebrafish	Rainbow Trout	1
	TOTAL	65

Table 3-7. Effect Categories represented in the database of UF_{Inter} point estimates.

Effect Endpoint Inclusiveness	Effect Category	Number of Database Records
Population-relevant	Growth	4
	Mortality/Survival	1
	Reproductive (functional)	15
	Developmental	10
Comprehensive (not also counted with Population-relevant effect endpoints)	Metabolic/Physiologic	13
	Genotoxicity	2
	Gross Pathology	3
	Reproductive (vitellogenin; hormone levels)	15
	Reproductive (sperm structure)	2
	TOTAL	65

Table 3-8. Final UF_{Inter} values (unitless) are based on percentiles of the UF_{Inter} point estimate distribution, and are used to derive water SVs to characterize CEC hazards to freshwater fish. The UF_{Inter} 25%ile and 75%ile values were used to derive SV_{HIGH} and SV_{LOW} point estimates, respectively.

Effect Endpoint Inclusiveness	SV Type	UF_{Inter} in SV Derivation	Effect Categories	N	Percentiles in UF_{Inter} Point Estimate Distribution	**Final UF_{Inter} Values (unitless)**
Population-relevant	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse population effects ARE NOT expected in wild fish	Behavioral Developmental Growth Reproductive Survival	30	99%ile = 35.0 95%ile = 19.0 90%ile = 10.7 75%ile = 4.80	**4.8**
Population-relevant	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse population effects ARE expected in wild fish			50%ile = 3.04 25%ile = 1.45 10%ile = 1.15 5%ile = 1.00 1%ile = 1.00	**1.5**
Comprehensive	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse effects in individual fish ARE NOT expected in the wild	All Effect Categories	65	99%ile = 352.0 95%ile = 50.8 90%ile = 30.3 75%ile = 8.87	**8.9**
Comprehensive	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse effects in individual fish ARE expected in the wild			50%ile = 3.29 25%ile = 1.50 10%ile = 1.20 5%ile = 1.10 1%ile = 1.00	**1.5**



3.4 Intra-Species Sensitivity

3.4.1 Purpose

The purpose of the Intra-Species Sensitivity UF is to quantify that portion of total extrapolation uncertainty attributable to differences in sensitivity between subclasses within a species. It is used to extrapolate exposure-effect relationships (expressed as a LOAEC/LOEC or NOAEC/NOEC) from a controlled laboratory study that tested for effects in one class of individuals within a fish species (defined by life stage or sex) to an adjusted effect concentration representative of potentially more sensitive classes of individuals in the aquatic system of interest.

3.4.2 Background

Ecotoxicologists have long recognized that sensitivity to chemical contaminants can vary between classes of individuals within a fish species, which is consistent with the practice of applying an uncertainty factor for protecting sensitive subpopulations in human health risk assessment (USEPA 1989). Fish life stages can differ in their susceptibility to adverse effects from chemical contaminant exposure (e.g., Brion et al. 2004, Galus et al. 2013a, Parrish et al. 1978, Staples et al. 2011). Based on earlier literature reviews of the effects of legacy contaminants, it is commonly assumed that early life stages are more susceptible to chemical impacts than later life stages (e.g., McKim 1977, Wheeler et al. 2014). However, this assertion is not supported as a general rule either in the CFED developed in this project (refer to Attachment 3-5) or in the database compiled for derivation of the UF_{Intra} (Attachment 4-2). Hence, no *a priori* assumption was made in this analysis that any life stage is necessarily more sensitive to CEC exposures than other life stages, as a general rule across all studies. For some CECs, the response magnitude of certain effect endpoints also differs between males and females in the same life stage (e.g., Lei et al. 2013, Madureira et al 2012, and Pawlowski et al 2004). The magnitude of the difference in susceptibility between life stages or between sexes may itself also vary with species.

This section describes methods used to estimate a numeric range of values from data provided in the literature, and provides final UF_{Intra} values to apply in SV derivations. Intra-species classes are defined in terms of life stage and sex. Life stage classes included: embryo, larva, juvenile, and adult. Sex classes were: female, male, both, or uncertain (not reported or immature).

3.4.3 UF_{Intra} Database - Data Inclusion Criteria

A database was developed specifically for the purpose of deriving and documenting UF_{Intra} point estimates (Attachment 3-5). The UF_{Intra} point estimates were quantified from individual publications that reported results in more than one intra-species class (defined in terms of either life stage or sex) after exposure in water to the same CEC. General inclusion criteria that are common across all three empirical UFs are provided in Section 3.1.4.

Inclusion criteria specific to the UF_{Intra} database are as follows:

- *Intra-Species Class:* A single experiment must evaluate for effects in at least two life stages or each of the two sexes; one database record is created for each unique pairing of classes (life stage versus life stage, or male versus female) and effect endpoints
- *Chemical Scope:* Assays testing CECs were included; legacy contaminants were excluded
- *Effect Concentration:*
    - Both LOAEC (adverse endpoints) and LOEC (non-adverse endpoints) effect concentrations were included in the UF_{Intra} point estimate calculations, in order to maximize the spread of the UF point estimate distribution
    - Only experiments that identify a LOAEC/ LOEC in both of the Intra-species Classes are included
- *Effect Category:* Specific effect endpoints do not have to be the same between the two classes in the paired assay, particularly between life stages
- *Effect Magnitude:* In both control and LOAEC/ LOEC exposure groups effect magnitudes must be reported separately for each intra-species class, in either tabular or graphic format, as either a median or mean value for the exposure group

3.4.4 UF_{Intra} Database Structure and Contents

The database is structured to develop a distribution of UF_{Intra} point estimates. The database is a flat file in MS Excel spreadsheet format. The UF_{Intra} database consists of 123 records extracted from 33 peer-reviewed, published papers.

Database fields are organized into the following groups: Study Design, Comparison Information, Computations, and Supporting Information. The following list provides specific fields included in each group:

Study Attributes
- CEC Category
- CEC
- Population-Relevant Effect (Y or N)
- Species (Common Name)
- Comparison Class ("Sex", "Life Stage")

Comparison Information
- Class 1 – Sex - M,F; Life Stage - E,L,J,A)[19]
- Class 1 – LOAEC/ LOEC (ug/L)
- Class 1 – Effect Category at LOAEC/LOEC
- Class 1 – Effect Endpoint(s) at LOAEC/LOEC
- Class 1 – Effect Data Presentation (G ="Graph" or T="Table or Text")
- Class 1 – LOAEC/LOEC Effect Magnitude
- Class 1 – Control Effect Magnitude
- Class 1 – Effect Magnitude at LOAEC/LOEC (as % difference from control)
- Class 1 – Effect Data Source in Paper
- Class 2 – Sex - M, F; Life Stage - E,L,J,A)
- Class 2 – LOAEC/LOEC (ug/L)
- Class 2– Effect Category at LOAEC/LOEC
- Class 2 – Effect Endpoint(s) at LOAEC/LOEC
- Class 2 - Effect Data Presentation (G ="Graph" or T="Table or Text")
- Class 2 – LOAEC/LOEC Effect Magnitude
- Class 2 – Control Effect Magnitude
- Class 2 – Effect Magnitude at LOAEC/LOEC (as % difference from control)
- Class 2 – Effect Data Source in Paper

Computations
- Class 1 – EPUC1 - Effect Magnitude per unit Concentration at LOAEC/LOEC
- Class 2 – EPUC2 - Effect Magnitude per unit Concentration at LOAEC/LOEC
- UF_{Intra} Point Estimate – Ratio of EPUCs (higher/lower)

Supporting Information
- Notes
- Publication Reference

Records in the UF_{Intra} point estimate database are uniquely identified based on: Publication Reference, CEC, Species, Comparison Class, Class 1, Class 1 Effect Endpoint(s), Class 2, and Class 2 Effect Endpoint(s). Each record conforms to data inclusion criteria (Sections 3.1.4, 3.4.3).

Represented in the UF_{Intra} point estimate database are:
- 38 individual CECs or commercial CEC mixtures tested in water exposures in multiple intra-species classes (Table 3-9);
- 21 CEC Categories (Table 3-9);
- 9 freshwater or brackish water fish species representing a variety of niches (Table 3-10; Attachment 3-5);
- 27 unique pairwise comparisons between intra-species classes (Table 3-10);
- 8 Effect Categories (Table 3-11).

3.4.5 UF_{Intra} Point Estimate Derivation

Aspects of UF derivation that are shared among all three empirical UFs are presented in Section 3.1.4.

A database was compiled to derive point estimates of UF_{Intra}. Information was extracted for quantifying this UF from published studies that reported LOAEC/ LOECs in more than one subspecies class in separate assays, after exposure in water to the same test chemical under the same experimental conditions (Attachment 3-5).

Only data for pairwise life stage or sex comparisons presented in an individual publication were added to the database. For comparisons between sexes, the same species and endpoint were evaluated. For comparisons between life stages, the same species was

[19]E – embryo, L – larva, J – juvenile, A – adult

evaluated, but the endpoint was not always the same between the two life stage assays. For instance, in a reproductive toxicity assay, the endpoint associated with the LOAEC/LOEC in adults may be number of eggs produced, while an endpoint associated with the LOAEC/LOEC in the embryo life stage may be survival. When different effect endpoints are evaluated in different intra-species classes, the effect magnitudes are not directly comparable. Hence, effect magnitudes in each UF_{Intra} database record were converted to percent difference from the negative control, where each species' subclass had its own exposure control group.

In each database record, relative sensitivity was represented in each of the tested intra-species classes using the ratio of the effect magnitude at the LOAEC/LOEC to the LOAEC/LOEC concentration for that intra-species class. The ratio is called the effect-per-unit-concentration (EPUC).

This approach differs from that used to derive UF_{CC} point estimates, where the concentrations and effect magnitudes of the highest exposure groups in paired single-CEC and mixture assays were utilized. For UF_{CC} derivations, only one or the other of the highest exposure groups was required to be a LOAEC/LOEC. In contrast, for UF_{Intra} derivations, the two different intra-species classes in each paired assay may have different intrinsic sensitivities to the tested CEC, so the LOAEC/LOEC values for each of the two intra-species classes were utilized.

In each record of the UF_{Intra} database, the pairwise comparison in sensitivity between intra-species classes (i.e., UF_{Inter} point estimate) was computed as follows:

1) The EPUC in the Class 1 assay was computed as:
   $EPUC_{Class\ 1}$ =
   Effect magnitude at $LOAEC/LOEC_{Class\ 1}$ /
   $LOAEC/LOEC_{Class\ 1}$

2) The EPUC in the Class 2 assay was computed as:
   $EPUC_{Class\ 2}$ =
   Effect magnitude at $LOAEC/LOEC_{Class\ 2}$ /
   $LOAEC/LOEC_{Class\ 2}$

where,

$LOAEC/LOEC_{Class\ 1}$ and $LOAEC/LOEC_{Class\ 2}$ are concentrations of the same CEC.

3) One UF_{Inter} point estimate was computed in each database record as:

$$UF_{Inter} = EPUC_A / EPUC_B$$

where,

$EPUC_A$ =
the greater value between $EPUC_{Class\ 1}$ and $EPUC_{Class\ 2}$

$EPUC_B$ =
the lesser value between $EPUC_{Class\ 1}$ and $EPUC_{Class\ 2}$

3.4.6 UF_{Intra} Point Estimates and Final Values

The UF_{Intra} point estimates are based on comparisons of relative sensitivity between paired assays in different intra-species classes. Apart from potential differences between life stage assays in exposure durations and effect endpoints evaluated, other study design elements were held constant between the paired assays.

Two UF_{Intra} point estimate distributions were developed. One distribution contains all of the point estimates in the database (Figure 3-5), and was used to obtain "comprehensive type" UF_{Intra} values for derivations of comprehensive SV_{HIGH} and SV_{LOW} values. The second distribution contains comparisons involving only population-relevant endpoints (i.e., behavioral, developmental, growth, reproductive, and survival) (Figure 3-6), and was used to obtain "population-relevant" UF_{Intra} values.

Values of both the comprehensive type UF_{Intra} and population-relevant UF_{Intra} point estimates range from 1 to 17,756. There were eight out of 123 UF_{Intra} point estimates that exceeded 100, but these database records did not appear to share common study designs with respect to species, effect endpoints or CECs (Attachment 3-5). Literature values of UF_{Intra} reported for legacy contaminants (see Table 3-1) were comparable to the values selected for CECs based on percentiles of empirical UF_{Intra} point estimate distributions (Table 3-12).

Specific percentiles of the comprehensive- and population-relevant UF_{Intra} point estimate distributions were selected for deriving SV_{HIGH} and SV_{LOW} point estimates (Table 3-12). Rationale for selected percentiles is provided in Section 3.1.4.2: Final Empirical UF Values as Distribution Percentiles.

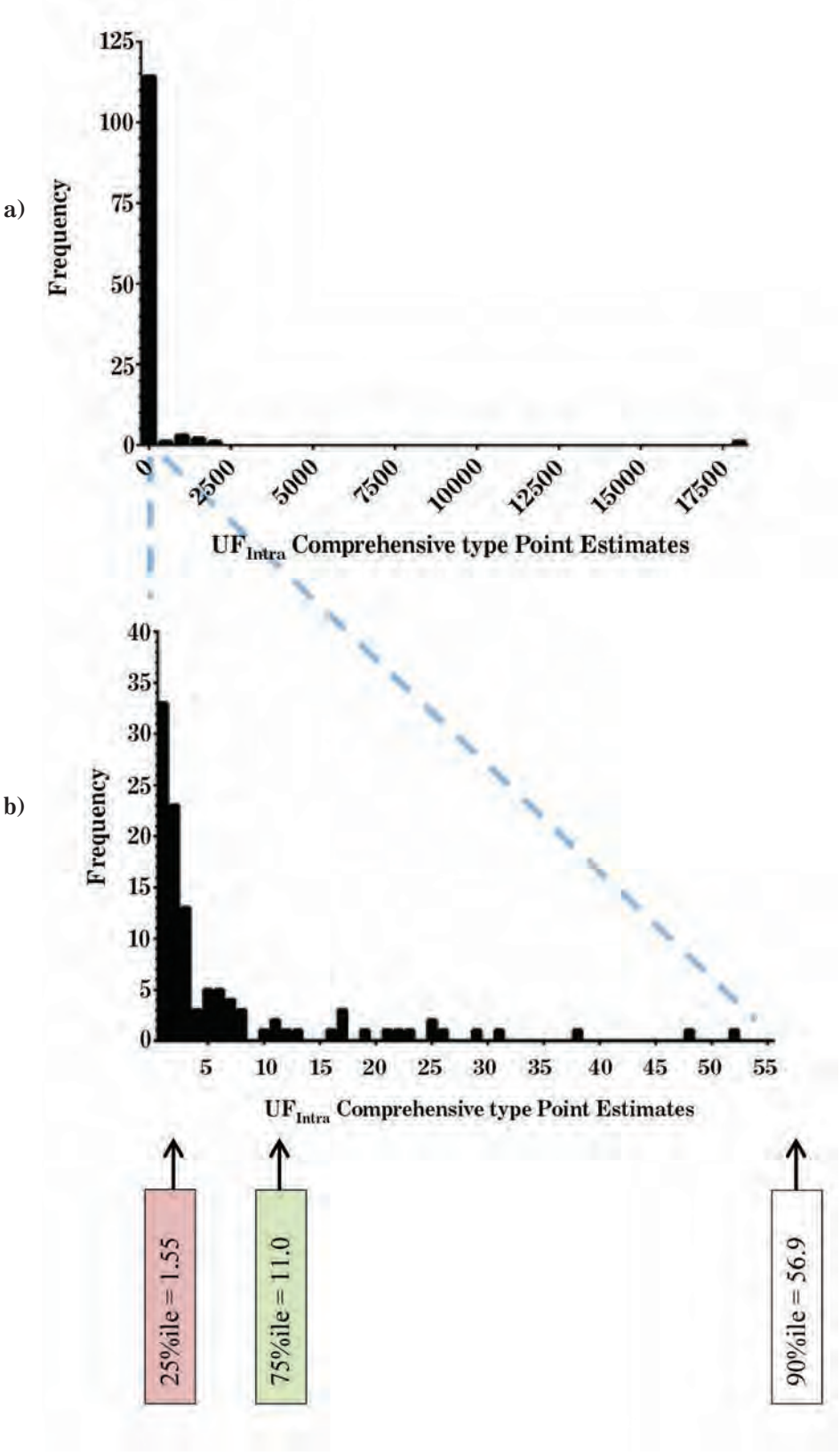


Figure 3-5. Frequency distribution of (a) all and (b) a focused subset of comprehensive type Intra-Species UF (UF_{Intra}) point estimates derived from data reported in publications that evaluate the same effects from exposure to a given CEC in two or more intra-species classes. Results from both sex and life stage comparisons are included. Selected percentiles of the distribution of all point estimates are indicated (N=123; min=1; max=17,756). The UF_{Intra} 25%ile and 75%ile values were used to derive comprehensive SV_{HIGH} and SV_{LOW} point estimates, respectively. X-axis values are mid-points of frequency distribution bin intervals.

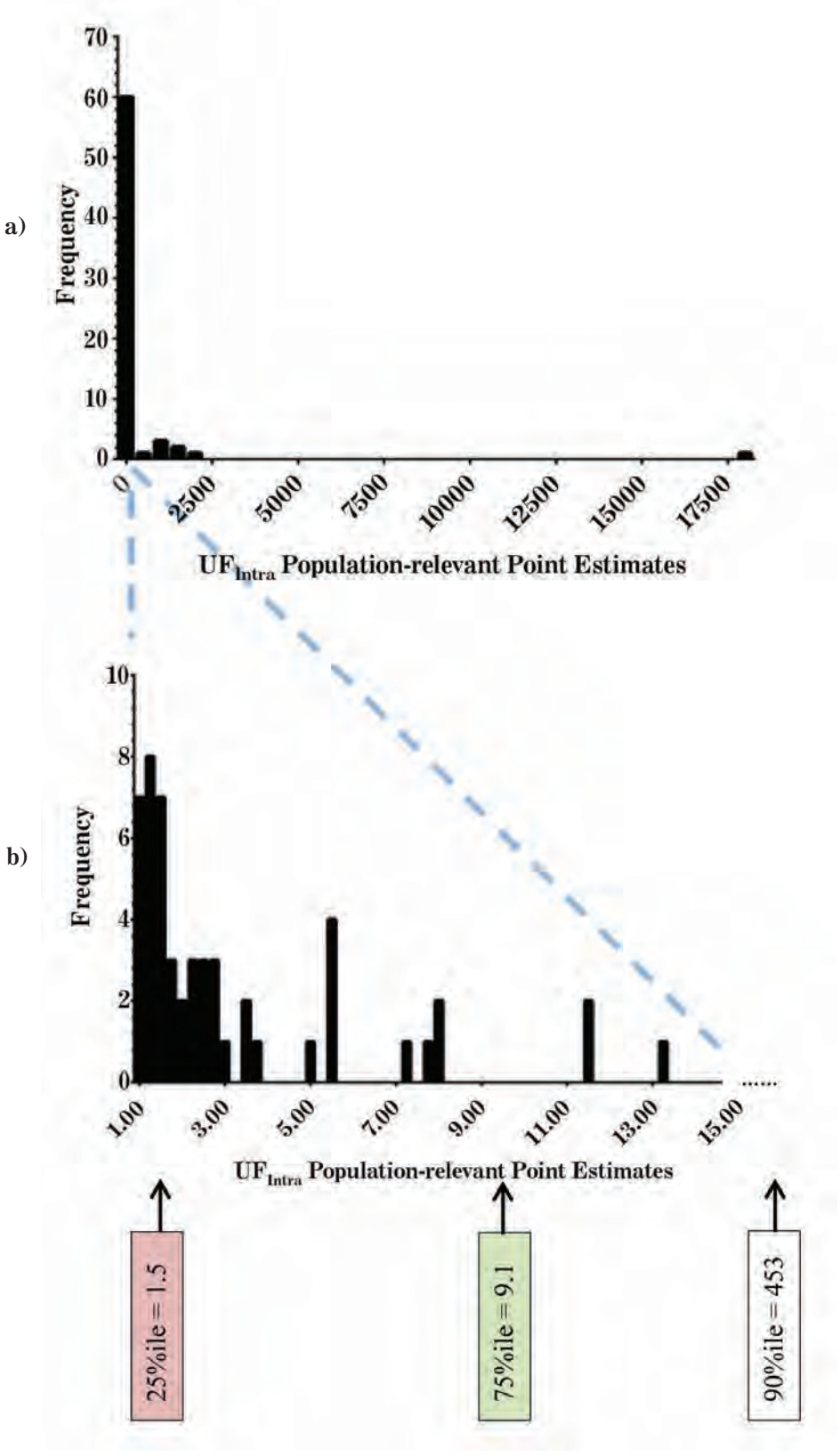


Figure 3-6. Frequency distribution of (a) all and (b) a focused subset of population-relevant Intra-Species UF (UF_{Intra}) point estimates derived from data reported in publications that evaluate the same effects (population-relevant adverse effect endpoints) from exposure to a given CEC in two or more intra-species classes. Results from both sex and life stage comparisons are included. Selected percentiles of the distribution of all point estimates are indicated (N=69; min=1; max=17,756). The UF_{Intra} 25%ile and 75%ile values were used to derive population-relevant SV_{HIGH} and SV_{LOW} point estimates, respectively. X-axis values are mid-points of frequency distribution bin intervals

Table 3-9. List of CEC Categories and individual CECs (and CEC mixtures) for which publications of laboratory studies were located that included parallel or sequential assays in two or more within-species classes.

CEC Category	CEC	Number of Database Records
Alkyl phenol	4-Nonylphenol	2
Flame Retardant	BDE-209	5
	DE-71	4
	triphenyl phosphate (TPP)	5
	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	7
Fungicide	Ronilan	1
	Vinclozolin	3
Herbicide	Trifluralin	3
Hormone	17a-ethinylestradiol (EE2)	7
	17a-methyltestosterone	3
	17B-estradiol (E2)	5
	Cyproterone acetate	6
	Dihydrotestosterone (DHT)	1
	Estriol (E3)	2
	Estrone (E1)	3
Plant hormone	B-sitosterol	4
Personal Care Product (antibacterial)	Triclosan	5
	Triclocarban	1
Pesticide	Pentachlorophenol	3
Pharmaceuticals - analgesic and anti-inflammatory	Acetaminophen	1
Pharmaceuticals - antibiotic	Sulfamethoxazole	1
	Trimethoprim	1
Pharmaceuticals - anticholesterol	Fenofibric Acid	1
Pharmaceuticals - anticonvulsant	Carbamazepine	3
Pharmaceuticals - antidepressant	Venlafaxine	2
Pharmaceuticals - antitumor - aromatase inhibitor	Fadrazole	1
	Letrozole	5
Pharmaceuticals - beta blocker - blood pressure suppressant	Propranolol Hydrochloride	2
Pharmaceuticals - lipid regulator	Gemfibrozil	1
Pharmaceuticals - NSAID	Ibuprofen	6
	Mefenamic Acid	3
	Naproxen	1
Plasticizer	Bisphenol A	13
	Tricresyl phosphate (TCP)	5
Surfactant	perfluorooctane sulfonate (PFOS)	4
Veterinary Hormone	B-Trenbolone	1
Wood Extractive	Betulinol (BET)	1
	Dehydroabietic Acid (DHAA)	1
	TOTAL	123

Table 3-10. Pairings of species' subclasses that were used to calculate UF_{Intra} point estimates. There were one or more database records for each type of pairing, associated with different CECs and/or effect endpoints.

Species (Common Name)	Comparison Class	Class 1 (Sex: **M**ale, **F**emale; Life Stage: **E**mbryo, **L**arva, **J**uvenile, **A**dult)	Class 2 (Sex: **M**ale, **F**emale; Life Stage: **E**mbryo, **L**arva, **J**uvenile, **A**dult)	Number of Database Records
Common Carp	Sex	M	F	2
Creek Chub	Sex	M	F	1
Fathead Minnow	Sex	M	F	14
	Life Stage	E	A	2
		E	J	1
		E	L	1
		J	A	1
		L	A	1
		L	J	5
Goldfish	Sex	M	F	1
Guppy	Sex	M	F	1
Japanese medaka	Sex	M	F	16
	Life Stage	A	E	6
		E	L	1
		J	A	2
		J	E	2
Mummichog	Sex	M	F	7
Sheepshead minnow	Life Stage	E	A	2
		E	J	2
		J	A	2
Zebrafish	Sex	M	F	37
	Life Stage	A	E	7
		A	L	1
		E	L	3
		J	A	2
		L	A	2
		L	J	1
			TOTAL	123

Table 3-11. Effect categories represented in pairwise comparisons of two different intraspecies classes (based on sex or life stage) in computation of UF_{Intra} point estimates.

Effect Endpoint Inclusiveness	Class 1 Effect Category	Class 2 Effect Category	Number of Database Records
Population-relevant	Behavioral	Behavioral	1
		Reproductive	1
	Developmental	Behavioral	1
		Developmental	1
		Growth	1
		Mortality/Survival	6
		Reproductive	12
	Growth	Growth	20
		Reproductive	1
	Mortality/Survival	Developmental	2
		Mortality/Survival	5
		Reproductive	3
	Reproductive	Developmental	1
		Mortality/Survival	1
		Reproductive	13
Comprehensive (not also counted with Population-relevant endpoints)	Gross Pathology	Gross Pathology	9
	Metabolic/Physiological	Metabolic/Physiological	13
	Neurological	Neurological	1
	Reproductive (blood/plasma reproductive hormones)	Reproductive (blood/plasma reproductive hormones)	26
	Reproductive (reproductive hormone production)	Reproductive (reproductive hormone production)	4
	Reproductive (secondary sex characteristics)	Reproductive (secondary sex characteristics)	1
		TOTAL	123

Table 3-12. Final UF_{Intra} values (unitless) are based on percentiles of the UF_{Intra} point estimate distribution, and are used to derive water SVs to characterize CEC hazards to freshwater fish. The UF_{Intra} 25%ile and 75%ile values were used to derive SV_{HIGH} and SV_{LOW} point estimates, respectively.

Effect Endpoint Inclusiveness	SV Type	UF_{Intra} in SV Derivation	Effect Categories	N	Percentiles in UF_{Intra} Point Estimate Distribution	**Final UF_{Intra} Values (unitless)**
Population-relevant	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse population effects ARE NOT expected in wild fish	Behavioral Developmental Growth Reproductive Survival	69	99%ile = 17,756 95%ile = 1304 90%ile = 452.9 75%ile = 9.12	**9.1**
Population-relevant	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse population effects ARE expected in wild fish			50%ile = 2.64 25%ile = 1.50 10%ile = 1.10 5%ile = 1.02 1%ile = 1.00	**1.5**
Comprehensive	SV_{LOW}	One of the UFs used to derive a water concentration below which adverse effects in individual fish ARE NOT expected in the wild	All Effect Categories	123	99%ile = 1840 95%ile = 452.9 90%ile = 56.9 75%ile = 11.0	**11**
Comprehensive	SV_{HIGH}	One of the UFs used to derive a water concentration above which adverse effects in individual fish ARE expected in the wild			50%ile = 2.64 25%ile = 1.55 10%ile = 1.11 5%ile = 1.05 1%ile = 1.00	**1.6**

3.5 Exposure Duration

3.5.1 Purpose

The purpose of the Exposure Duration UF (UF_{Dura}) is to extrapolate exposure-effect relationships (expressed as a LOAEC or NOAEC) from a controlled laboratory study that tested for effects after acute or subchronic exposures to an adjusted effect concentration after chronic exposure.

3.5.2 Background

Early human health risk assessment guidance recommends applying an uncertainty factor specifically to account for exposure duration extrapolations (USEPA 1989). Likewise, it is well-established in ecotoxicology that there is a negative relation between exposure duration and the LOAEC (e.g., USEPA 1997). That is, LOAECs after acute exposures typically occur at greater water concentrations than after subchronic exposure, and subchronic LOAECs generally are greater than chronic LOAECs. USEPA (1997) summarizes several reviews of this phenomenon in laboratory mammals exposed to legacy contaminants.

For the purposes of this document, we applied the following definitions to exposure durations in fish:

- Acute: <7 days exposure
- Subchronic: 7 – 28 days exposure
- Chronic: >28 days exposure

A classic definition of "chronic" exposure is a duration of ≥10% of the life span of the organism (Suter 1993). However, our CEC Ecotoxicity Database currently includes studies on 20 fish species, and more species will be included as additional CECs are added to the database. This large number of species, plus the consideration that life span may vary with sex, renders application of this definition unmanageable in our evaluation. Acute assays typically expose fish for 24, 48, 72, 96, or 120 hours (i.e., up to 5 days), and a recommended acute exposure duration in fish for laboratory studies is at least 96 hours (>4 days) (USEPA 1996b). Based on these guideposts, we defined acute exposure in the CFED as <7 days. Subchronic/ chronic exposure was simply defined as non-acute, or, the converse of acute exposure (≥7 days).

We used recommended experimental designs for fish toxicity assays as guideposts to identify a reasonable threshold exposure duration between subchronic and chronic exposures . Recommended exposure durations for test species in the early life stage toxicity test range from 28 to 60 days (USEPA 1996c). For many experimental fish species, recommended exposure duration in the partial life cycle test includes approximately 21 days of exposure in the F0 generation followed by a few days to up to 4 weeks of exposure in the F1 generation (OECD 2008). The full life cycle test is a chronic exposure assay, exposing fish from the beginning of one life stage through the same life stage one generation later (e.g., egg to egg) (USEPA 1996d). Our selected definition of >28 days for chronic duration incorporates all of these standard ecotoxicity tests in fish.

The UF_{Dura} was applied to LOAECs and NOAECs associated with acute or subchronic exposure assays in adults or juveniles, which are life stages that persist longer than 28 days in the majority of fish species. Although the entire duration of the embryo or larval life stage is often well within subchronic or acute exposure durations, effect concentrations were not adjusted with respect to exposure duration for early life stage exposures.

For adult and juvenile fish, ecotoxicity literature searches were focused on locating studies that evaluate effects of CECs in fish after subchronic or chronic exposure. The majority of records in the CFED reflect chronic exposures. However, there are certain important effect endpoints in adults and juveniles that are typically evaluated after shorter exposure periods, and these endpoints were not excluded from the databases based strictly on exposure duration. For example, assays that evaluate oxidative stress, gene expression, certain behavioral endpoints, and certain physiological endpoints (e.g., gill ventilation) are often evaluated after short-duration exposures. For the most part, these effect endpoints would not be considered population-relevant by our working definition (see Section 2.5, Figure 2-2, and Attachment 2-1 for further discussion of population-relevance). However, wherever assays with short exposure durations were included in order to capture certain effect endpoints, often there were other endpoints – some of them population-relevant (e.g., mortality) - that also were evaluated in the same assays and were included in the CFED and were used to derive SVs.

Raimondo et al. (2007) summarized the literature on acute-to-chronic ratios (ACRs) of LOAECs for a variety of legacy contaminants in aquatic organisms. In fish, the 10th and 90th percentiles were found to be 2.7 and 90, respectively, with a minimum of 1.2 and median value of 9.3 (Raimondo et al. 2007). In an earlier review, Lange et al. (1998) summarized percentiles of the ratios of fish acute EC50/chronic NOEC in 55 legacy organic contaminants. The 50th and 90th percentiles were found to be 5.53 and 24.2 in halogenated organics, 6.4 and 21.8 in aromatic hydrocarbons, and 12.98 and 71.2 in pesticides, while the 50th percentile of the ACR in "other organics" was 2.21. Focusing on the lethality endpoint, Mayer et al. (1994) estimated the 97th percentile of the chronic/acute ratio in fish for 18 legacy contaminants to be approximately 3.6. In human health risk assessment, Dourson et al. (1996) summarized empirical subchronic to chronic ratios from toxicity assays reported in several reviews, and reported average ratios between two and three, and a 95th percentile of approximately 10. In a focused review of mammalian oral toxicity assays in six chlorinated volatile legacy contaminants, subchronic/ chronic ratios were ≤ 3.5 (Kadry et al. 1995).

No review of ACR values in fish was located for CECs. As the fish ecotoxicity literature on CECs continues to expand, ratios of this type may form the basis for an empirical derivation of UF_{Dura} for CECs, possibly by CEC Category, in future updates of this document.

3.5.3 UF_{Dura} Final Values

The CEC SVs developed in this document are used to assess hazard to fish from long-term continuous or repeated (high frequency) exposures in fish, such as may occur in waterbodies that receive continuous discharges, or persistently episodic discharge or runoff containing CECs.

Guidelines for UF_{Dura} values (Table 3-13) were developed using literature reviews and precedent reviewed above. Selected values of UF_{Dura} range from one to five, which fall within the range of ecotoxicity and human health risk assessment values for this UF for legacy contaminants (see Table 3-1, Raimondo et al. 2007, Lange et al. 1998, Dourson et al. 1996, Kadry et al. 1995, Mayer et al. 1994). However, selected values do not reflect extreme UF values in the reported ranges for legacy contaminants. The values are distributed on an ordinal scale, and assigned based on the difference in assay duration between the empirical short-term and the target duration of ≥ 28 days in fish juveniles or adults. At this time, the selected maximum value of five is recommended where the assay exposure is less than one day. However, with very few exceptions our CFED systematically excluded short-term exposure assays, and such short duration single exposures may not be common in environmental exposure scenarios. Thus, the scaling of UF_{Dura} to assay duration may be revisited in future revisions of this document.

3.6 Effect Concentration

3.6.1 Purpose

The purpose of the Effect Concentration UF (UF_{Conc}) is to extrapolate an unbounded LOAEC determined in a controlled laboratory study to an estimated corresponding NOAEC for the same chemical and endpoint, in the same species and life stage.

3.6.2 Background

The rationale for using LOAEC and NOAEC values as effect concentration metrics throughout this CEC toxicity assessment is provided in the description of Effect Concentrations in the CFED (Section 2.4).

Chapter 4 describes the derivation of SV_{LOW} values, which are concentrations of dissolved CEC in water below which negligible hazard to fish is anticipated. The input to deriving an SV_{LOW} point estimate is a NOAEC, which may be either bounded or unbounded (see definitions in Section 2.4.1). However, some records in the CFED report only an unbounded LOAEC, where no NOAEC is reported. An SV_{LOW} point estimate may be derived from an adjusted NOAEC, which is obtained by applying the UF_{Conc} to an unbounded LOAEC. The UF_{Conc} *is not applied* in the derivation of SV_{HIGH} point estimates, where the effect concentration input to the derivation process is a LOAEC.

There is considerable precedent for the application of the UF_{Conc} in regulatory toxicology of legacy contaminants, in both human health and ecological contexts. The U.S. Department of Health and Human Services, Centers for Disease Control, Agency for Toxic Substances and Disease Registry (ATSDR) derives Minimal Risk Levels (MRLs) for "evaluating public health risks associated with exposure to hazardous substances" (Pohl and Abadin 1995). During MRL derivation, ATSDR uses a UF "…to account for uncertainties associated with extrapolation from a LOAEL to a NOAEL…." The USEPA utilizes an UF "…to account for the uncertainty involved in extrapolating from LOAELs to NOAELs…" in the derivation of reference doses (RfDs) for evaluating risk from oral exposure to a chemical in human health risk assessments (Barnes and Dourson 1988, USEPA 1989, USEPA 1993b). The European Union applies a number of assessment factors, including a LOAEL-to-NOAEL factor, to human and animal toxicity data to obtain a "derived no-effect level" (DNEL) for chemical hazard assessment for workers and the general public (ECETOC 2010).

Table 3-13. Application guidance for the Exposure Duration UF (UF_{Dura}).

Source of Uncertainty	UF_{Dura} Value Assignment Conditions Based on Data in the CEC Fish Ecotoxicity Database	UF_{Dura} Values for Deriving SVs
EXPOSURE DURATION	Extrapolation of exposure-effect relationships (expressed as a LOAEC or NOAEC) from a controlled laboratory study that tested for effects after acute or subchronic exposures to an adjusted effect concentration after chronic exposure	
	More than 4 weeks (>28 days) of exposure involving fish exposed only as adults or only as juveniles; all tests involving exposure of only embryo or only larval stages in individual fish; all tests involving exposures in more than one life stage in individual fish	1
	1 to 4 weeks (7 – 28 days) in adults or juveniles	2
	1 to 7 days in adults or juveniles	3
	Less than 24 hours in adults or juveniles	5

In human health risk assessment, the LOAEL NOAEL uncertainty factor has been estimated empirically. Among assays conducted with six chlorinated volatile organics, 91% of the LOAEL/NOAEL ratios were ≤ 6 (Kadry et al. 1995). Dourson and Stara (1983) reviewed the history of the use of uncertainty factors in human health risk assessment, and found that the LOAEL/NOAEL ratio was five or less for 96% of the chemicals reviewed. In a subsequent review of science-based UFs in non-cancer human risk assessment, Dourson et al. (1996) indicate that the data support LOAEL-NOAEL UFs ≤10, while the USEPA (1997) acknowledged that multiplying a LOAEL by 0.1 is "standard practice."

Considerably less information is available regarding LOAEC-NOAEC adjustment in ecological hazard assessment. In their review of uncertainty factors that have been used in EHAs for legacy contaminants, Duke and Taggert (2000) found that values of UF_{Conc} ranged from 2 to 55 (see Table 3-1). No study comparing paired chronic LOAEC to NOAEC values for legacy or emerging contaminants was located in fish ecotoxicity literature.

3.6.3 UF_{Conc} Final Values

Guidelines for UF_{Conc} values (Table 3-14) were developed based on precedent in human health and ecological risk assessment (see above). We did not locate a review of LOAEC-NOAEC comparisons in CEC assays in fish, so we provisionally accepted the results of Dourson and Stara (1983) as a guide to specify a maximum UF_{Conc} value of five (Table 3-14). This value was the 95th percentile of LOAEL/NOAEL ratios in their review of toxicology assays in legacy contaminants conducted for human health risk assessment. The selected maximum falls at the lower end of the range of guidelines and historical usage in legacy contaminant ERAs (Table 3-1; Duke and Taggart 2000).

Levels of UF_{Conc} below the maximum value of five that are provided in Table 3-14 simply reflect ordinal levels of combined uncertainty from both LOAEC-NOAEC extrapolation and nominal-measured concentration differences. The analysis provided below provides some justification for including the nominal-measured concentration distinction in the UF_{Conc} guide.

No review of the relationship between nominal and measured concentrations in fish exposed to aqueous contaminants was located, nor did we locate a precedent for adjusting for this source of extrapolation uncertainty. However, a number of studies included in the CFED reported both nominal and measured concentrations at each exposure level (Bjerregaard et al. 2008, Flinders et al. 2014, Galus et al. 2013, Hatef et al. 2012, Hua et al. 2013, Imai et al. 2007, Ishibashi et al. 2004, Ji et al. 2013, Kang et al. 2002, Li et al. 2009, Li et al. 2010, Li et al. 2011, Mandich et al. 2007, Mihaich et al. 2012, Morthorst et al. 2013, Olsen et al. 2014, Orvos et al. 2002, Overturf et al. 2012, Schultz et al. 2012, Sohoni et al. 2001, Staples et al. 2011, van den Brandhof and Montforts 2010, Yokota et al. 2000 and Zenobio et al. 2014). We compiled all of the nominal-measured paired concentrations reported in these studies into a single database (N= 101), and computed percent difference of measured concentrations from nominal concentrations, as follows:

$$\% \left[\frac{\text{Measured} - \text{Nominal}}{\text{Nominal}} \right] \times 100\%$$

The data compilation (Figure 3-7) provided the following results:

- Nominal concentrations overestimate measured concentrations (measured < nominal) in 78% of observations, and underestimate in 21%.
- Percent difference of measured from nominal concentration is ≤ 25% (+ or -) in 71% of observations.
- Percent difference of measured from nominal concentration is ≤ 50% (+ or -) in 88% of observations.
- Measured is more than 100% greater than nominal in only 3% of observations.

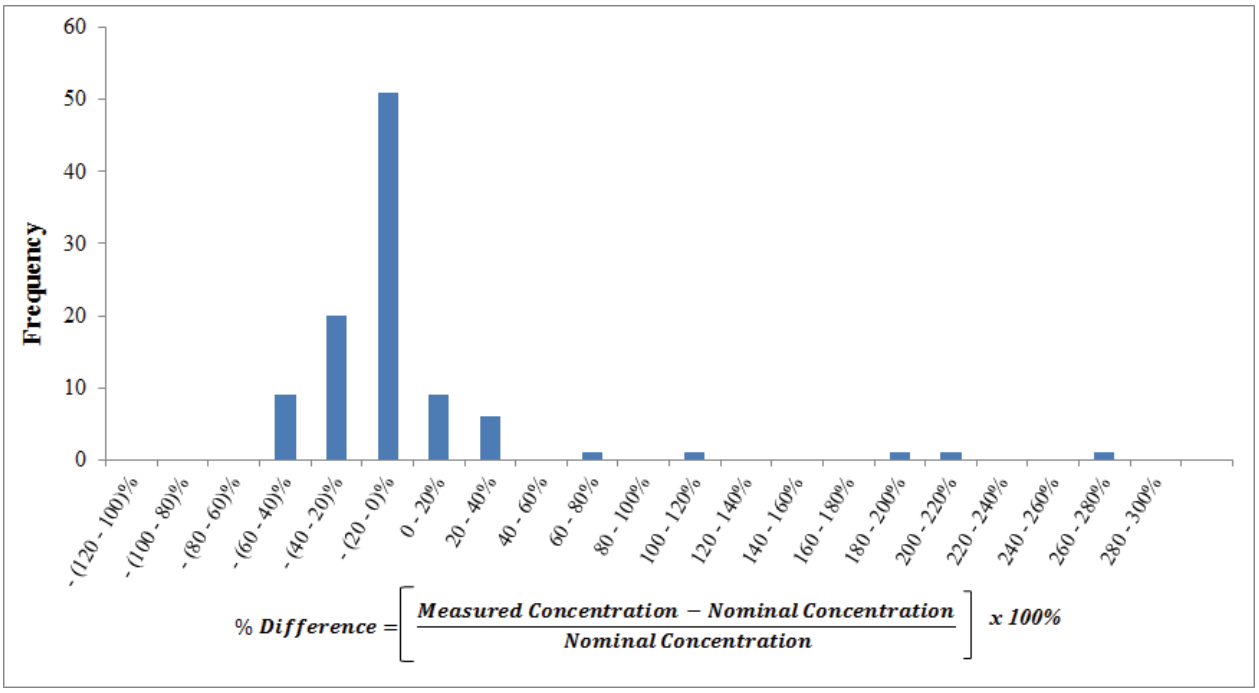


Figure 3-7. Frequency distribution of percent difference of measured concentrations from nominal concentrations reported in 24 publications included in the CEC Fish Ecotoxicity Database.

Table 3-14. Application guidance for the Effect Concentration UF (UF_{Conc}).

Source of Uncertainty	Description	Selected UF_{Conc} Values for Deriving Low SVs
EFFECT CONCENTRATION[20]	Extrapolation from LOAEC to NOAEC for the same endpoint, species, life stage, and exposure duration. This UF is only used to derive SV_{LOW} point estimates.	
Bounded or unbounded NOAEC based on *measured* exposure concentrations is available		1
No measured NOAEC is available, but a bounded or unbounded NOAEC based on *nominal* exposure concentrations is available		2
No NOAEC is available, but an unbounded LOAEC based on *measured* exposure concentrations is available		3
No NOAEC is available, but an unbounded LOAEC based on *nominal* exposure concentrations is available		5

[20]In this report, EC_X and LC_X were not used to derive SV_{Low} values, but may be considered in future updates. Effect Concentration $(EC)_X$ values identify an estimated exposure concentration resulting in a specified prevalence of an effect in tested individuals; it is an exposure concentration that would result in observed adverse effects in 'X' percent of exposed individuals (LC_X is an EC_X, where the effect endpoint is lethality).

3.7 Database Adequacy

3.7.1 Purpose

The purpose of the Database Adequacy UF (UF_{Data}) is to account for uncertainty associated with limited quantity and breadth of reliable and available ecotoxicity information. Differences between CECs in the richness of available published information are reflected in the number of Effect Categories represented in the CFED. The CEC-specific UF_{Data} values are used to extrapolate from the geometric mean among effect-specific SVs to CEC-specific mean SVs (Figure 1-2; also refer to Figure 4-1).

3.7.2 Background

There are few precedents for the database adequacy UF in derivation of ecotoxicity thresholds in the U.S. In USEPA human health dose-response assessments for the derivation of an RfD, a modifying factor "… is sometimes used which is based on a professional judgment of the entire data base of the chemical" (USEPA 1989, USEPA 1993b). European Union guidance for computing derived no effect levels (DNELs) includes the application of an assessment factor for "quality of the 'whole' database" (ECETOC 2010). Incorporation of UF_{Data} into CEC SV derivations is consistent with these precedents.

The UF_{Data} is the only uncertainty factor that is not applied during derivation of SV point estimates. For both population-relevant and comprehensive SVs, the process of deriving SV_{HIGH} and SV_{LOW} values from literature-reported effect concentrations results in three sets of products (Figure 1-2; refer to Section 4.3): SV Point Estimate Distributions, Effect Category-Specific SVs, and mean SVs. The UF_{Data} is applied during the last derivation step, moving from Effect Category-Specific SVs to mean SVs (see Section 4.3.4).

3.7.3 UF_{Data} Final Values

The UF_{Data} values are applied using a simple system. The basis for assigning UF_{Data} values for a CEC was the number of Effect Categories for which a LOAEC or NOAEC was reported in the CFED. Since the number of Effect Categories differed in the derivations of population-relevant and comprehensive SVs, there are two sets of UF_{Data} assignment guidance and values (Table 3-15). CEC-specific UF_{Data} values for deriving mean SV_{LOW} values are provided in Table 3-16; UF_{Data} values for deriving SV_{HIGH} values for each CEC are provided in Table 3-17.

Table 3-15. Application guidance for the Database Adequacy UF (UF_{Data}).

Source of Uncertainty	UF Value Assignment Conditions Based on Data in the CEC Fish Ecotoxicity Database	UF Values for Deriving SVs
Database Adequacy (Comprehensive type)	Breadth of endpoints considered for determining this UF include all Effect Categories for which effects endpoints in fish were evaluated in controlled lab studies for the chemical of interest. This UF is applied to the geometric mean of effect-specific SVs to compute the Mean Comprehensive Screening Value.	
	More than four effects categories have SV point estimates, for the given CEC	1
	Three or four categories have SV point estimates, for the given CEC	3
	One or two effect categories have SV point estimates, for the given CEC	5
Database Adequacy (Population-relevant)	Breadth of endpoints considered for this UF are limited to endpoints within the following population-relevant Effect Categories that could be readily used to model impact to survival and propagation: Growth, Developmental, Reproductive, Survival/Mortality, Behavioral (only as pertaining to endpoints directly relevant to adult survival, reproduction, or recruitment of next generation breeders - such as ability to escape predators or capture food, breeding behavior, or nesting behavior.	
	Four or more effects categories have SV point estimates, for the given CEC	1
	Two or three categories have SV point estimates, for the given CEC	2
	Only one Category has a SV point estimate; only Survival/Mortality, for the given CEC	3
	Only one Category has a SV point estimate; not Survival/Mortality, for the given CEC	5

Table 3-16. Database Adequacy UF values for deriving SVLOW values, based on the number of Effect Categories in the CEC Fish Ecotoxicity Database reporting a NOAEC or an unbounded LOAEC. Some, but not all, endpoints in the population-relevant (P) Effect Categories were determined to be population-relevant; total numbers of eligible records for each Effect Category are listed in the comprehensive type (C) rows.

Population-relevant (P); Comprehensive(C)	Effect Categories	Number of Records with an Unbounded LOAEC or a NOAEC (bounded or unbounded) in the CEC Fish Ecotoxicity Database, by CEC													
		Androstene-3,17-dione, 4-	**Bisphenol A**	**Carbamazepine**	**Citalopram**	**DEET**	**Diphenhydramine**	**Estrone**	**HHCB**	**Ibuprofen**	**Lidocaine**	**Sitosterol, beta-**	**TBEP**	**Triclosan**	**Venlafaxine**
P	Behavioral		1	6	5		1	2	1	1	1	2	1	6	3
P	Developmental		23	6			1	6	2	3		4	2	5	3
P	Growth	1	8	3		2			1	2		3		3	1
P	Mortality		7	2		3		1	1	4		1	1	2	1
P	Reproductive	2	13	2		1		4		3		5		3	2
C	Behavioral		1	7	5		1	2	1	1	1	5	1	6	3
C	Developmental		26	6			1	6	2	3		4	3	5	3
C	Growth	1	8	3		2			1	2		3		3	1
C	Mortality		7	2		3		1	1	4		1	1	2	1
C	Reproductive	2	15	2		1		4	1	4		8		3	2
C	Cancer														
C	Circulatory/ Blood Constituents			2		1				1		2			
C	Endocrine/ Hormone					1				1					1
C	Genotoxicity									1				1	
C	Gross Pathology		2												
C	Histopathology			2		1				1				1	2
C	Immunological					1									
C	Neurological			2											
C	Physiological/ Metabolic			4		1		2	1	1					
Population-relevant Database Adequacy UF Values		**2**	**1**	**1**	**5**	**2**	**2**	**1**	**1**	**1**	**5**	**1**	**2**	**1**	**1**
Comprehensive type Database Adequacy UF Values		**5**	**1**	**1**	**5**	**1**	**5**	**1**	**1**	**1**	**5**	**1**	**3**	**1**	**1**

Table 3-17. Database Adequacy UF values for deriving SV$_{HIGH}$ values, based on the number of Effect Categories in the CEC Fish Ecotoxicity Database reporting a LOAEC (either bounded or unbounded). Some, but not all, endpoints in the population (P) Effect Categories were determined to be population-relevant; total numbers of eligible records for each Effect Category are listed in the comprehensive type (C) rows.

Population-relevant (P); Comprehensive (C)	Effect Categories	Number of Records reporting a LOAEC (bounded or unbounded) in the CEC Fish Ecotoxicity Database, by CEC													
		Androstene-3,17-dione, 4-	Bisphenol A	Carbamazepine	Citalopram	DEET	Diphenhydramine	Estrone	HHCB	Ibuprofen	Lidocaine	Sitosterol, beta-	TBEP	Triclosan	Venlafaxine
P	Behavioral		1	6	2		1	1	1		1	2	1	4	3
P	Developmental		18	5			1	4	1	2		3	2	4	
P	Growth	1	1	1					1						
P	Mortality		2	1		2			1	3				1	1
P	Reproductive		13	2				4		3		2	1	1	2
C	Behavioral		1	6	2		1	1	1		1	2	1	4	3
C	Developmental		20	5			1	4	1	2		3	3	4	
C	Growth	1	1	1					1						
C	Mortality		2	1		2			1	3				1	1
C	Reproductive	2	15	2				4	1	4		4	1	1	2
C	Cancer														
C	Circulatory/ Blood Constituents			2		1				1		2			
C	Endocrine/ Hormone					1				1					1
C	Genotoxicity									1					
C	Gross Pathology		1												
C	Histopathology			2											1
C	Immunological														
C	Neurological			2											
C	Physiological/ Metabolic			4				2	1	1					
Population-relevant Database Adequacy UF Values		**5**	**1**	**1**	**5**	**3**	**2**	**2**	**1**	**2**	**5**	**2**	**2**	**1**	**2**
Comprehensive type Database Adequacy UF Values		**5**	**1**	**1**	**5**	**3**	**5**	**3**	**1**	**1**	**5**	**3**	**3**	**3**	**1**

3.8 Cumulative Uncertainty

The SV point estimates were developed in individual records of the CFED by dividing cumulative UF ($UF_{\prod}$) values into LOAECs or NOAECs. Cumulative UF values are aggregations of individual UF values that are associated with separate sources of uncertainty: Chemical Complexity (UF_{CC}), Inter-species Sensitivity (UF_{Inter}), Intra-species Sensitivity (UF_{Intra}), Effect Concentration (UF_{Conc}), and Exposure Duration (UF_{Dura}). Each component UF value, in turn, reflects assay conditions from which corresponding effect concentrations were generated. Thus, each $UF_{\prod}$ is paired with a specific effect concentration to produce one SV point estimate. Since separate sets of UF values were developed for deriving SV_{HIGH} and SV_{LOW} point estimates (see Table 3-2), sources of uncertainty were aggregated to obtain separate cumulative UFs for deriving SV_{HIGH} values ($UF_{\prod\text{-}High}$) and SV_{LOW} values ($UF_{\prod\text{-}Low}$).

Systematic interactions or correlations between sources of extrapolation uncertainty have not been described for CEC effects in fish. In the absence of contrary information, we adopted the conservative assumption that sources of uncertainty vary independently of each other, which is consistent with risk assessment guidance from regulatory agencies (e.g., USEPA 1989). Thus, sources of uncertainty were aggregated as the simple multiplication product of UF values across sources of uncertainty, as follows:

For deriving SV_{HIGH} point Estimates:

$$UF_{\prod\text{-}High} = UF_{CC\text{-}High} * UF_{Inter\text{-}High} * UF_{Intra\text{-}High} * UF_{Dura\text{-}High}$$

For deriving SV_{LOW} point Estimates:

$$UF_{\prod\text{-}Low} = UF_{CC\text{-}Low} * UF_{Inter\text{-}Low} * UF_{Intra\text{-}Low} * UF_{Dura\text{-}Low} * UF_{Conc}$$

Multiplication of UFs is conservative because it maximizes the numeric value of cumulative uncertainty given the component UF values. This conservatism in computation is partially offset by the fact that each component UF value was near the low end of the corresponding overall range of values. For UF_{CC}, UF_{Inter} and UF_{Intra} , the final values were quartiles of UF point estimate distributions with values that generally occurred near the low end of the distributions (see Figures 3-1 through 3-6). For UF_{Conc} and UF_{Dura}, our selected range of values was near the low end of comparable UF values reported in the literature for legacy contaminants (compare Tables 3-13 and 3-14 against Table 3-1).

Uncertainty due to Database Adequacy (UF_{Data}) was not included in the derivation of SV point estimates (see Figure 1-2; Section 3.7), and so is not aggregated with the other UFs to obtain $UF_{\prod}$ values.

In individual records of the CFED, separate $UF_{\prod}$ values were computed for up to four types of SV point estimates (population-relevant SV_{HIGH}; population-relevant SV_{LOW}; comprehensive SV_{HIGH} or comprehensive SV_{LOW}), using record-specific values for each UF (Attachments 4-2A, B, C, and D, respectively). Actual ranges of $UF_{\prod}$ values utilized in the derivations of the four SV types were:

- Population-relevant $UF_{\prod\text{-}High}$: 2.475 – 7.425 (Figure 3-8),
- Population-relevant $UF_{\prod\text{-}Low}$: 78.6 – 1179.4 (Figure 3-9),
- Comprehensive $UF_{\prod\text{-}High}$: 2.64 – 13.2 (Figure 3-10), and
- Comprehensive $UF_{\prod\text{-}Low}$: 195.8 – 2937 (Figure 3-11).

Two clear patterns emerge from these ranges. First, as a group, $UF_{\prod\text{-}High}$ values are at least an order of magnitude lower than $UF_{\prod\text{-}Low}$ values, and second, the breadth of $UF_{\prod\text{-}High}$ values is much smaller than the range of $UF_{\prod\text{-}Low}$ values. However, there was no consistent relationship in magnitudes of paired $UF_{\prod}$ values and SV point estimates. That is, large $UF_{\prod}$ values were not consistently related to low SV values, and small $UF_{\prod}$ values were not consistently related to high SV values (see Figures 3-8 to 3-11).

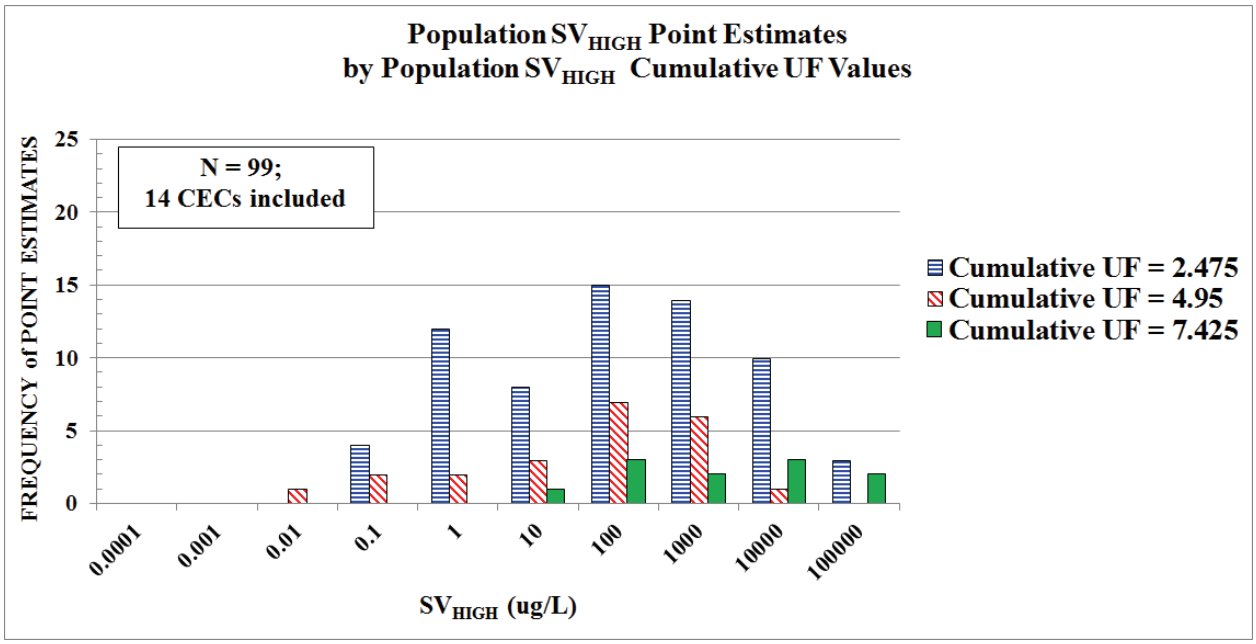


Figure 3-8. Frequency distribution of population-relevant SVHIGH point estimate values as related to cumulative UF values used to derive the SVHIGH values. This graphic illustrates that the magnitude of cumulative UF does not introduce systematic bias into population-relevant SVHIGH point estimate values. X-axis values are upper bounds of x-axis frequency distribution bin intervals.

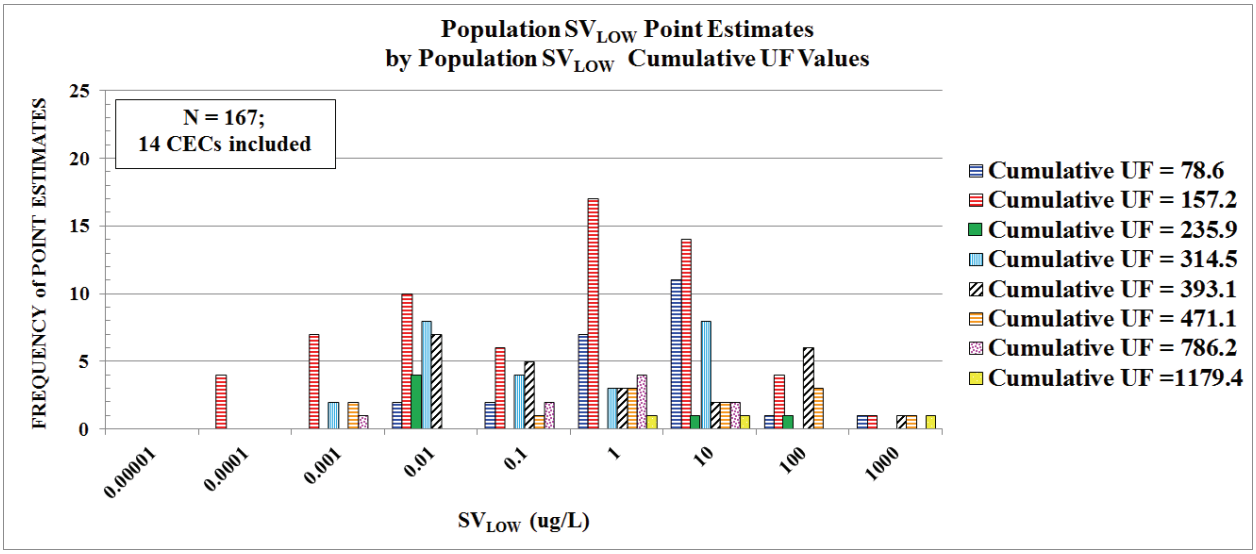


Figure 3-9. Frequency distribution of population-relevant SVLOW point estimate values as related to cumulative UF values used to derive the SVLOW values. This graphic illustrates that the magnitude of cumulative UF does not introduce systematic bias into population-relevant SVLOW point estimate values. X-axis values are upper bounds of frequency distribution bin intervals.

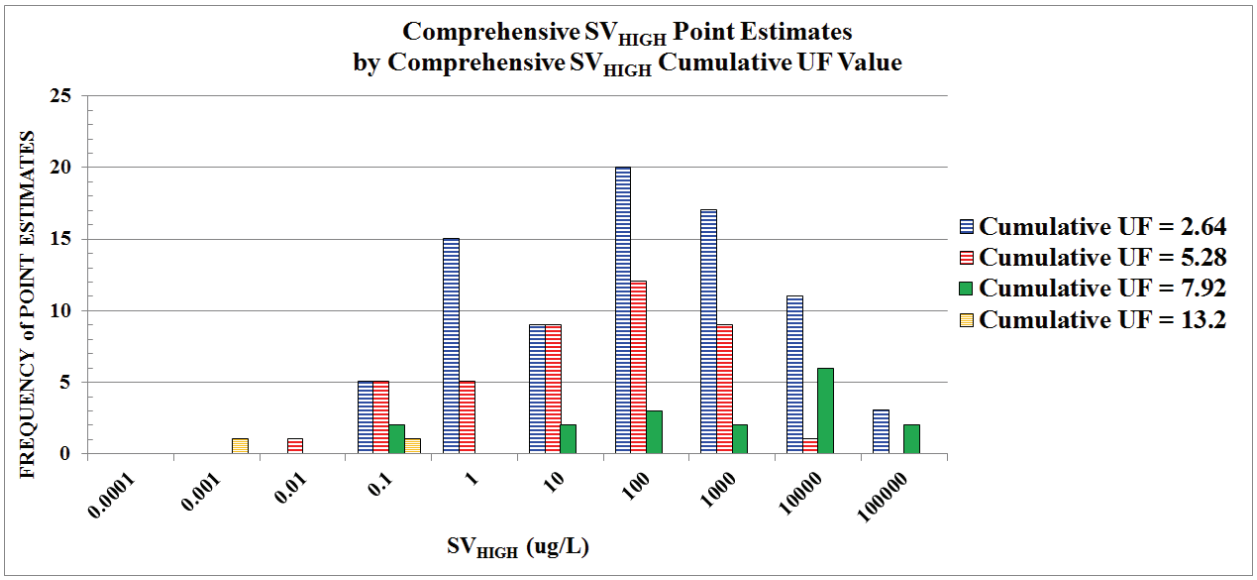


Figure 3-10. Frequency distribution of comprehensive SVHIGH point estimate values as related to cumulative UF values used to derive the SVHIGH values. This graphic illustrates that the magnitude of cumulative UF does not introduce systematic bias into comprehensive SVHIGH point estimate values. X-axis values are upper bounds of frequency distribution bin intervals.

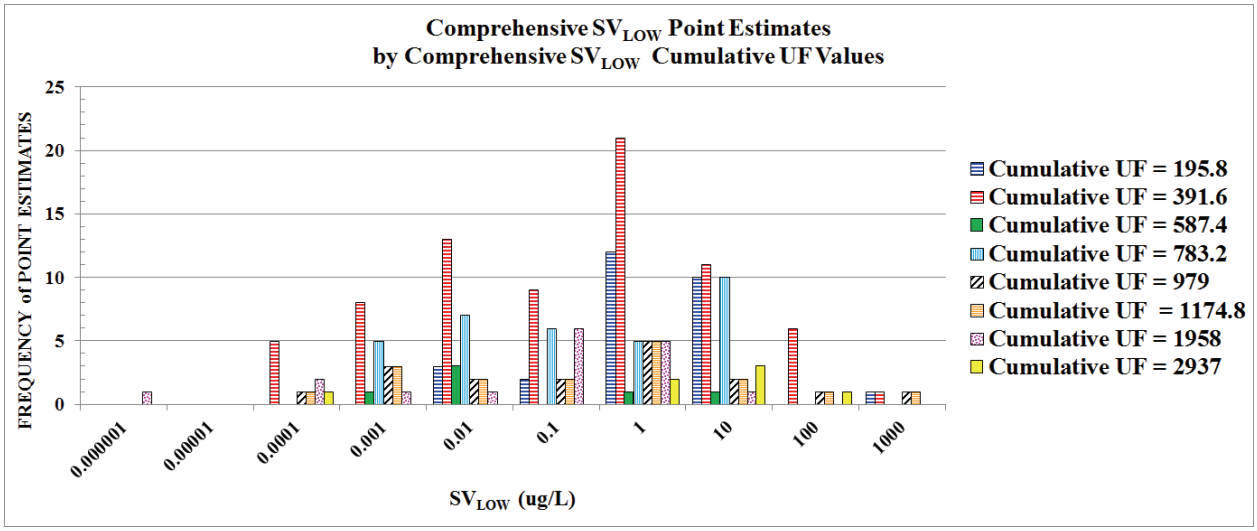


Figure 3-11. Frequency distribution of comprehensive SVLOW point estimate values as related to cumulative UF values used to derive the SVLOW values. This graphic illustrates that the magnitude of cumulative UF does not introduce systematic bias into comprehensive SVLOW point estimate values. X-axis values are upper bounds of frequency distribution bin intervals.

3.9 Modifying Factors

The purpose of the Modifying Factor (MF) is to provide, on a case-by-case basis, an opportunity for risk assessors to account for additional known or suspected sources of uncertainty in a particular lab-to-environmental effects extrapolation that were not addressed elsewhere in Chapter 3. These are either additional sources of uncertainty that have not already been explicitly accounted for in the uncertainty factor derivations or, in the opinion of the practitioner, instances where the derived values were not sufficiently conservative given circumstances of the particular application. Additional sources of uncertainty may be associated with receptor characteristics, exposure differences, environmental stressors, or other factors that may render receptor species more susceptible to adverse effects from contaminant exposure than the tested species, but for which insufficient literature data were available to quantitatively estimate an empirical UF.

The SVs presented in Chapter 4 were derived using the UFs developed in Chapter 3, but the SV derivations did not involve an MF. The CEC uncertainty factors were applied on a record-by-record basis in the ecotoxicity database to obtain SV point estimates. Specific UF values applied are partially based on the type of SV that was being derived (see Table 3-2).

For example:

- *Receptor:* Highly unusual life history, morphological, behavioral, or physiological characteristics in target, resident fish species that are not represented among the test species in the literature used to derive the UF_{Inter} (see Attachment 3-4). Such as, an extremely long life span (>70 yrs) and late age at sexual maturity (>20 yrs in females) in lake sturgeon that deviate significantly from the relatively short-lived species used to derive values for UF_{Inter}.
- *Stressor:* Non-contaminant stressors (e.g., pH, DO, temperature, turbidity, water velocity, and forage availability and/or quality) may increase receptor susceptibility in various ways, such as increasing physiological stress and reducing energy reserves. If non-contaminant stressors are measured or estimated in the environment at levels that diverge significantly from the range of laboratory conditions under which the experiments to derive SVs were conducted, it would be appropriate to apply an MF.
- *Exposure:* Unusual environmental exposure scenario, such as acute spikes, repeated, or intermittent environmental exposure, in contrast to lab study conditions of continuous or renewal, subchronic or chronic exposures used to derive the SVs.

The SVs may be adjusted for application-specific conditions using the MF, as follows:

$$SV_{adj} = SV / MF.$$

The practitioner may use any MF value, but the rationale for the type(s) and magnitude of uncertainty addressed by the MF should be documented. Specific values are assigned by professional judgement on a case-by-case basis, and may depend on factors such as:

- the number and degree of unaccounted-for uncertainty sources,
- the degree that field conditions deviate from design characteristics or test conditions in experiments that were represented in the CFED (Chapter 2) or UF databases (Sections 3-2, 3-3, 3-4),
- the presence in the CFED of at least one LOEC value that is regarded by the practitioner as sufficiently adverse to include in the SV derivation, and that is a lower concentration than any of the LOAECs used to derive the SV. Although LOECs were included in the CFED, they were not used to derive SVs.

The MF may be applied to both the SV_{LOW} and SV_{HIGH}, as circumstances of the particular application suggest, but the different hazard interpretations of SV_{LOW} and SV_{HIGH} values should be considered.

CHAPTER 4 - SURFACE WATER CEC SCREENING VALUES for FRESHWATER FISH ECOLOGICAL HAZARD ASSESSMENT

4.1 Purpose

The CEC SVs presented in this chapter are principally intended to be used as decision-making resources. Grounded in empirical ecotoxicity information, they comprise a flexible set of guidance values to facilitate CEC relative hazard assessment. Appropriate applications of CEC SVs are intended to provide researchers and resource managers with reliable information to rank alternative actions and prioritize activities with respect to potential CEC impacts in fish.

The CEC SVs presented here should not be misinterpreted as regulatory values or absolute toxicity thresholds. The USFWS does not have the authority to establish national regulatory screening values for contaminants, and estimation of absolute toxicity thresholds was not one of the goals of this project.

4.2 Background

Hazard screening values are an end product of the Toxicity Assessment portion of a chemical ecological hazard assessment (Figure 1-1). Surface water CEC SVs are estimated concentrations of chemicals in water that demarcate expectations about adverse effects in target biota under field conditions. Representations of either measured or modeled contaminant concentrations in surface water comprise the corresponding Exposure Assessment portion of a chemical ecological hazard assessment for surface water. The SVs described in this chapter were developed to screen CEC concentrations in surface water in order to evaluate relative CEC hazard potential in freshwater fish. Laboratory studies used to derive the SVs reported aqueous CEC concentrations. Therefore, when the CEC SVs are applied in an EHA, the Exposure Assessment should generate measured or modeled dissolved CEC in water for hazard screening. Hazard scores may be developed and used to rank relative hazard between sampling sites, between CECs, and between sampling events at specific sampling sites.

The CEC SV concentrations generally fall between the chemical's water solubility at the high end, and limits of detection at the low end. Currently there are no excursions at the high end of the SV range, and only a few excursions at the low end of the SV range (e.g., comprehensive SV_{LOW} for estrone), but it is anticipated that if improvements in CEC analytical method sensitivity continue into the future, detection limits will eventually fall below lower bound SVs.

These SVs are not intended to provide an understanding of absolute hazard or risk. Actual absolute ecotoxicity thresholds may be lower than the mean SVs, because:

- the breadth and depth of appropriate information in the literature varies considerably between CECs; there are many important datagaps that, if filled, may result in a decrease (or increase) in SV estimates,
- derivation of empirical UFs utilized information from limited datasets, and effect endpoints were unevenly represented in the UF datasets, so UFs may underestimate adjustments for various sources of uncertainty, and
- derivation steps for UFs (Chapter 3) and SVs (Section 4.3) utilized either percentiles or metrics of central tendency of distributions rather than extreme values, so the most conservative effect concentrations, which may be more reflective of absolute toxicity thresholds, were not used.

Chapters 2 and 3 described the input information for deriving CEC SVs. Chapter 2 introduced how information from the literature was organized into a database structured to provide NOAECs and LOAECs for derivation of SV point estimates (see Figure 2-1). Chapter 3 presented the UFs used to adjust NOAEC or LOAEC values for various sources of lab-to-field extrapolation uncertainty, including the derivation of several empirically-based UFs.

4.2.1 Existing Surface Water Screening Values

Surface water screening values for legacy chemical hazard assessments in aquatic systems have been developed for purposes associated with several U.S. and international authorities. These authorities include: Clean Water Act (CWA); Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Resource Conservation and Recovery Act (RCRA); Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); as well as State regulations (e.g., NYSDEC 2016), European Chemical Bureau Directives (e.g., ECB 2003), and Environment Canada and Climate Change regulations (e.g., CCME 2007b). Regulatory programs have included the derivation and applications of aquatic SVs for legacy contaminants under various names (refer to Table 1-1).

Functionally, there are two basic types of chemical contaminant SVs. The first type of contaminant SV is a lower bound concentration, below which significant adverse impacts are not expected in receptor taxa. We refer to a lower bound concentration is a "SV$_{LOW}$". Typically, this type of SV is used to identify chemicals, sampling locations, receptor taxa, or chemical uses (such as future pesticide uses) that do not require further scrutiny in the ecological risk assessment process if measured or predicted concentrations fall below the SV. In the U.S. and the European Union, examples of existing lower bound threshold SVs for legacy contaminants include:

- *Ecological Screening Values* developed by USEPA Region 4 for application at hazardous waste sites (USEPA 2015b),
- *Aquatic Life Benchmarks* for prospective pesticide hazard assessment developed by the USEPA Office of Pesticide Programs (USEPA 2004), and
- *Probable No Effect Concentrations* (PNECs), used for prospective hazard assessments in the European Union (ECB 2003).

The second group of SVs is comprised of upper bound concentrations, above which it is reasonable to expect adverse impacts. We refer to this type of SV is a "SV$_{HIGH}$". Under certain statutory or regulatory authorities, a management action may be triggered if a sufficient number and/or severity of excursions from this upper bound threshold are observed. Example SVs in this category includes the following for legacy contaminants:

- *Great Lakes Water Quality Criteria* (USEPA 1995),
- *USEPA Aquatic Life Ambient Water Quality Criteria* (USEPA 2016b),
- *New York State Water Quality Standards* for individual substances (NYSDEC 2016)
    - Similar water quality criteria or standards have been adopted for implementation by other states
- *Ecotox Thresholds* for application at Superfund sites (USEPA 1996a).

In the U.S., environmental regulations for CECs are very limited. Lists of emerging contaminants and CEC analytical methods include 4-nonylphenol, which is the only CEC for which a regulatory water quality criterion has been finalized in the United States, to date. A draft white paper entitled *Aquatic life criteria for contaminants of emerging concern: Part I - General challenges and recommendations* (USEPA 2008a) was submitted by the USEPA Office of Water/ Office of Research and Development Emerging Contaminants Workgroup to the USEPA Science Advisory Board (SAB) for review in 2008.

Although the SAB responded with comments and recommendations (USEPA 2008b), guidance for developing aquatic life AWQCs for CECs has not yet been issued by the USEPA.

The majority of existing CEC SVs available in the scientific literature (Attachment 4-1) are probable no effect concentrations (PNECs), most of which were developed and applied in the European Union (EU) (ECB 2003). Many PNECs rely on acute ecotoxicity data and/or modeled effect levels (e.g., Ginebreda et al. 2009, Sanderson et al. 2003) in a wide array of aquatic taxonomic groups. One derivation method for PNECs utilizes a species sensitivity distribution (SSD) to determine a "hazardous concentration" (HCp) (e.g., Caldwell et al. 2012, Capdevielle et al. 2008, Wright-Walters et al. 2011). To develop the SSD, effect concentrations in water for various aquatic species are plotted on concentration in water. The HCp is identified using the SSD, and represents a water concentration that may adversely affect a certain percentage (p) of species in an aquatic community. Hence, a PNEC based on this derivation method is not intended to be protective of the most sensitive species, but rather may be protective of approximately (1-p)*100% of the species in the system. At the discretion of the investigator, an "assessment factor", often a value of 1000, may be divided into the HCp to account for uncertainties inherent in the HC estimate – in particular, the acute-to-chronic exposure duration extrapolation (e.g., Park and Choi 2008). A PNEC based on an HCp is derived only if a chemical has a sufficient number of relevant effect concentrations reported in the literature for multiple species.

Additional CEC SV derivation approaches represented in the literature, and identified in Attachment 4-1, include:

- EU PNECs derived from the lowest effect concentration located in the literature, with the application of a generic safety factor (e.g., Carlsson et al. 2006, Ferrari et al. 2004, Halling-Sorensen et al. 2000, Oehlmann et al. 2008, Park and Choi 2008, Zhao et al. 2010);
- EU Environmental Quality Standards (EQSs) derived from relevant PNECs (e.g., Hansen 2007);

- Canadian Water Quality Guidelines (e.g., BCME 2009, MOEE 1994)
- US Ambient Water Quality Criterion for 4-nonylphenol (USEPA 2005)

4.2.2 Classic SV Derivation Paradigm

A classic approach for deriving aquatic screening values for legacy contaminants broadly resembles the following:

1. Define the purpose of the SV
2. Define the scope:
   a. Ecological receptor taxa (e.g., aquatic biota),
   b. Effect endpoints (e.g., population-relevant endpoints),
   c. Contaminant (e.g., future-use pesticides, CECs),
   d. Exposure duration (e.g., acute or chronic),
   e. Exposure medium (e.g., surface water, sediment, biota tissue),
3. Consult appropriate ecotoxicological databases and reviews for relevant exposure-effect information (e.g., TOXLINE, ECOTOX);
4. Compile relevant exposure-effect information from the literature;
5. For lower bound SVs:
   a. As needed, derive surrogate effect concentration values estimated with quantitative models, such as ECOSAR (Mayo-Bean et al. 2012), for chemicals that do not have sufficient empirical information reported in the literature;
   b. Identify the critical effect concentration from among reported empirical and modeled effect concentrations (often, the lowest relevant LOAEC or NOAEC, or, HC*p* if using a SSD);
   c. Either adopt the critical effect concentration itself as the SV, or apply uncertainty factors to obtain a single SV for the chemical;
6. For upper bound SVs:
   a. Utilize central tendency values (e.g., geometric means or median values) calculated from the effect concentration dataset compiled from studies in target taxa or modeled effect concentrations (e.g., USEPA 1985).

4.2.3 Variations on the Classical Theme: Our Overall Approach for Deriving CEC SVs

Our approach to deriving CEC SVs (Figure 4-1; also see Figure 1-2) is an adaptation of the classic approach for deriving legacy contaminant SVs as outlined above. The CEC SV derivation approach includes the following features:

1. This analysis focused on the potential f*or adverse effects in freshwater fish from chronic, aqueous exposures to CECs in surface water*, rather than all aquatic receptors and exposure durations;
2. *Only empirical results* from published lab studies in fish were used - no modelled effect concentrations were used;
3. *Empirical CEC UFs* were derived for several sources of uncertainty (see Chapter 3) ;
4. *A distribution of SV point estimates* was obtained from sets of chronic adverse effect concentrations (LOAEC or NOAEC, as appropriate) recorded in CFED records, by applying uncertainty factors appropriate to the study conditions (Section 4.3.2; Figures 4-1 and 4-2). In contrast, the classic paradigm obtains a single SV point estimate, with or without application of UFs, by either:
   a. selecting a single critical effect concentration from a single study as the basis for a single SV (e.g. – the lowest NOAEC in the database), or
   b. using a central tendency estimate, or percentile, of effect concentrations (NOAECs and/or LOAECs) across studies as the basis for deriving a single SV
5. A total of *twelve SV products for each* CEC was developed (see Section 4.4, Attachment 4-2, and Tables 4-1a to 4-1d) – that is, all twelve permutations of the following factors:
   a. *Type of SV:* SV$_{HIGH}$ or SV$_{LOW}$;
   b. *Effect Endpoint Inclusiveness:* Population-relevant or Comprehensive, and
   c. *Degree of Information Aggregation:*
      i. Point estimate distributions,
      ii. Effect-specific SV values, or
      iii. Mean SV values.

4.3 CEC SV Derivation Methods

4.3.1 Scope

Screening values were developed for the chronic exposure of fish to emerging contaminants in surface water, as measured in the aqueous phase. Numeric values of SVs are provided for 14 CECs that were among the most commonly detected in surface water during 2010-2012 at USFWS sampling sites distributed across the U.S. Great Lakes Basin (Attachment 1-1; also see Choy et al. 2017; Lee et al. 2012). Ecotoxicity literature searches were completed for 25 of the most frequently detected CECs. No fish ecotoxicity studies were located for nine of the 25 most frequently detected CECs, and two CECs did not have sufficient information to derive a pair of mean SVs (both SV_{HIGH} and SV_{LOW}) (see Attachment 1-1).

For each CEC, three different SV products were developed sequentially from effect concentrations recorded in the CFED, in increasing degree of aggregation:

1. SV point estimates were derived from published effect concentrations (LOAECs and NOAECs) by application of uncertainty factors,
2. Effect-specific SVs were developed from corresponding SV Point Estimate distributions, and
3. Mean SVs were developed from Effect-Specific SV distributions.

The SVs were derived from published exposure-effects information (with very few exceptions, as noted in the database). Effect concentrations were compiled in the CFED (Chapter 2) for either obligate or facultative freshwater fish species that inhabit freshwater at least part of their life cycle (Table 4-2). Inclusion criteria for assays used to derive CEC SVs are provided in Section 2.2.

For each CEC, both SV_{HIGH} and SV_{LOW} estimates were derived from two sets of suborganism- and organism-level effect concentrations (Figure 4-2): (1) a focused set of population-relevant effect concentrations and (2) all (comprehensive) effect concentrations. Distributions of unadjusted effect concentrations that were used to derive point estimates for population-relevant SV_{HIGH}, population-relevant SV_{LOW}, comprehensive type SV_{HIGH} and comprehensive type SV_{LOW} are provided in Figures 4-3, 4-4, 4-5 and 4-6, respectively. Effect concentrations in these distributions range across 7 to 9 orders of magnitude.

It is likely that, for some CECs – particularly CECs that accumulate significantly in biological tissue - SVs developed using methods described in this document are conservative with respect to potential for impact to target fish. Technically, our CEC SVs may be used to assess only that portion of total hazard attributable to aqueous exposure to dissolved CEC. However, at a given dissolved CEC concentration in the surface water of the subject system, actual exposure occurs not only via direct uptake of the dissolved CEC via gills and integument, but also uptake via ingestion of water and potentially contaminated prey and incidental ingestion of benthic and/or suspended particles. Controlled laboratory studies that provide quantitative exposure-effects data for ingestion exposures of CECs in fish are very rare in the literature, so ingestion exposure could not be incorporated explicitly into CEC SV derivations. Thus, application of the CEC SVs does not account for total exposure or assess total potential impact. This underestimate of total hazard also may vary due to biological factors, such as trophic position (e.g., primary versus higher order consumers), principal prey base (e.g., omnivore, piscivore, insectivore, or molluskivore) and trophic niche (e.g., benthic versus pelagic feeder) of target fish species.

Mean SVs cannot be used to interpret definitively the totality of CEC-related hazard to fish. They are not absolute toxicity thresholds. However, as with existing legacy screening values (see Table 1-1), these CEC SVs are based on a thorough review of the best available empirical information. Appropriately applied, this toolset is a flexible decision-making aid for assessing relative hazard to fish and for prioritization of research or management action alternatives between sites or systems.

Derivation methods, the rationale for developing each class of SV, and their uses, are provided in Sections 4.3.2 – 4.3.4.

4.3.2 CEC SV Point Estimate Distributions

Derivation

Surface water SV point estimates were derived from dissolved CEC adverse effect concentrations (i.e., NOAECs and LOAECs) that were compiled in the CFED (Figures 4-3 to 4-6). Each record in the CFED contains effect concentration information for only one CEC and only one Effect Category, evaluated in a single published assay. Database records are further differentiated in terms of relative adversity of effect concentrations (see Attachment 2-1 for discussion of effect adversity). One of the following types of effect concentrations is reported in each CFED record:

- Bounded LOAEC with the corresponding bounded NOAEC,
- Unbounded LOAEC,
- Unbounded NOAEC,
- Bounded LOEC with the corresponding bounded NOEC,
- Unbounded LOEC, or
- Unbounded NOEC.

Only effect concentrations for adverse effect endpoints (LOAECs and NOAECs) were used to derive SV point estimates (Figure 4-2). Effect endpoints that were considered to be adverse for the purpose of SV derivation are identified in Attachment 2-1. The

SV point estimates were computed by applying corresponding sets of UF values (see Tables 3-4, 3-8, 3-12, 3-13 and 3-14) aggregated as cumulative UFs. Only one adverse effect concentration per database record was used to derive a given SV Point Estimate[21] .

Screening value point estimates are computed by dividing empirical adverse effect concentrations by corresponding cumulative UF values:

SV_{HIGH} Point Estimate = LOAEC / $UF_{\prod\text{-High}}$, and

SV_{LOW} Point Estimate = NOAEC (or, LOAEC) / $UF_{\prod\text{-Low}}$

where, $UF_{\prod}$ = cumulative uncertainty.

Sources of uncertainty included in cumulative uncertainty calculations, and computation of cumulative UF values from study-specific information in each record in the CFED, are described in Section 3.8. A full description of types of UFs that comprise the cumulative UF is provided in Chapter 3.
For each population-relevant NOAEC, both population SV_{LOW} and comprehensive SV_{LOW} point estimates were derived (Figure 4-2). However, the two SV_{LOW} point estimates, which were based on the same NOAEC value, would have different magnitudes because cumulative UFs used to derive the SV_{LOW} point estimates differ between comprehensive- and population-relevant empirical UFs. Similarly, for each population-relevant LOAEC, resulting population SV_{HIGH} and comprehensive type SV_{HIGH} point estimates have different values due to different magnitudes of UFs.

Point estimate SV distributions for 14 CECs are illustrated in Section 4.4; all SV Point Estimate values are provided in Attachment 4-2.

Rationale

Controlled, peer-reviewed laboratory studies comprised a reasonably reliable information base concerning the occurrence and severity of effects in fish due to CEC exposures. The vast majority of studies used in CEC SV derivations reported in this document are peer-reviewed, providing a measure of assurance against unreliable information. Exposure-effect information reported in these studies is the basis for the CEC SV derivations.

Rather than selecting a single critical effect concentration from which to derive mean SV values, uncertainty factors were applied to individual effect concentrations to obtain SV point estimates (Attachment 4-2). Literature NOEAC and unbounded LOAEC values were used to compute SV_{LOW} point estimates (Figures 4-4 and 4-6), from which mean SV_{LOW} values were ultimately obtained. Similarly, LOAECs in the database that were used to derive SV_{HIGH} point estimates (Figures 4-3 and 4-5) were adjusted individually with the appropriate set of uncertainty factors (Figure 4-2). Attachment 4-2 provides the actual effect concentration, uncertainty factors, and SV value for each SV point estimate developed in this document.

Screening value point estimates were developed from each adverse effect concentration in the CFED for several reasons, including:

- *Flexibility:* The sequential aggregation of SV information from Point Estimates to Effect-Specific SVs to pairs of mean SVs (see Figures 1-2 and 4-1) provides flexibility in possible applications this is not possible with classic single-value SVs.
- *Transparency:* The SV point estimate distribution approach is comprehensive and transparent, allowing practitioners to grasp quickly the ecotoxicological basis for each mean SV (see individual CECs in Section 4.4).
- *Explicit Representation of Multiple Receptors Including Most Sensitive tested Species:* The distributions of SV point estimates explicitly contain information from all species for which data were located. A common approach in ecological risk assessment is to select a single critical effect concentration from the database (such as the lowest NOAEC, or the 5th percentile in a distribution of effect concentrations) as the basis for deriving a single lower bound SV value, appears to have been borrowed from human health risk assessment. In human health risk assessment, however, there is a single, very well-described target receptor species – humans. In human health toxicity assessment, the relative merits of each individual toxicity assay are evaluated in the light of the entire literature database, to identify a critical effect concentration for derivation of a single chemical toxicity threshold value. The most appropriate and

[21]For example, suppose a single record provides both a bounded LOAEC and a bounded NOAEC for adverse effect endpoints in the Reproductive effect category. Since reproductive effects are relevant at both the individual and population levels of ecological organization, point estimates for both the population-relevant SV_{HIGH} and comprehensive SV_{HIGH} would be derived by application of corresponding UFs to the bounded LOAEC reported in that record. Likewise, point estimates for both the population-relevant SV_{LOW} and comprehensive SV_{LOW} would be derived by application of corresponding UF values to the bounded NOAEC in that record.

As a further example, suppose a record reports an unbounded NOAEC for adverse effect endpoints in the Histopathology effect category (see Attachment 2-1). Histopathologies are considered adverse at the individual fish level of ecological organization, but are not considered population-relevant in the sense that they are not readily, quantitatively modeled with respect to impacts to survival or propagation of populations. Hence, a comprehensive SV_{LOW} point estimate would be derived from the unbounded NOAEC by application of appropriate UFs, but no population-relevant SV_{LOW} point estimate and no SV_{HIGH} estimates would generated from this record. Conversely, if the record contained only an unbounded LOAEC for histopathologies, then both comprehensive SV_{HIGH} and SV_{LOW} point estimates would be derived from this record (see Figure 4-2).

defensible effect concentration is selected. This intensive selection process is much easier to conduct in human health toxicity assessment than in ecological toxicity assessment, in which the target species may be unknown (e.g., the most sensitive species in the system), or the target taxa are diverse (e.g., all fish species, or all aquatic biota).

- *Data Inclusiveness:* There is uncertainty regarding the relevance of published laboratory studies to the potential for impacts in fish in natural systems (see Chapter 3). For data-rich CECs, selecting the critical effect concentration from which to derive a SV_{LOW} should take into consideration both the magnitudes of the effect concentrations, and the relative reliability of the exposure-effect information - evaluated across studies. However, assessing the relative data quality and reliability of information across all of the available studies is beyond the scope of this analysis. So, all adverse effect concentrations were included in SV derivation.
- *Reliability:* Taxonomic relatedness and chemical mode of action are likely to affect reliability of predicted hazardous concentrations (Raimondo et al. 2010). This fact complicates reliable selection of the most appropriate single study from among multiple fish taxa and selecting the critical effect concentration to use for deriving a single SV for a CEC.
- *Interpretability:* In an ecological toxicity assessment that utilizes UFs, an overly simple approach to selecting critical effect concentrations may result in an ambiguous result. For instance, the lowest NOAEC may not always provide the lowest possible SV_{LOW} point estimate. Since UF magnitudes can vary between studies, a high NOAEC may estimate a lower SV_{LOW} point estimate than a lower NOAEC (see Attachment 4-2). Similarly, the highest LOAEC may not result in the highest SV_{HIGH}.
- *Resiliency of Mean SVs:* The SV point estimate distribution approach utilizes the entire database of adverse exposure-effects information, as opposed to relying on the relevance of a single critical effect concentration. For data-rich CECs, mean SVs based on distributions of SV point estimates are somewhat resilient to the addition of newly published effect concentrations to the database. Approaches that select a single critical effect concentration may be more susceptible to significant changes in magnitude as new published information becomes available. Resilient mean SVs based on extensive databases may appeal to natural resource, water quality, and waste managers.

Utility of CEC SV Point Estimate Distributions

Probabilistic EHAs have been used in both site-specific retrospective situations and prospective EHAs (e.g., Berninger et al. 2011, Brain et al. 2006, Dobbins et al. 2009, Duvall and Barron 2000, Hall et al. 1997, Sanderson et al. 2003). There is growing interest in the ecotoxicological community to develop toxicity threshold values based on distributions of effect concentrations for use in probabilistic ecological hazard assessments (e.g., Belanger et al. 2015, Berninger and Brooks 2010). Chemical toxicity distributions may be used either in the toxicity assessment portion of the ERA to identify ecotoxicity benchmark concentrations based on percentiles of the distributions, or during hazard characterization to interpret the probability of specific kinds of effects at given exposure levels. Chemical toxicity distributions are distributions of effect concentrations, which are not individually adjusted for sources of uncertainty, but specific percentiles of this distribution may be divided by a generic UF (often referred to as an assessment factor) to obtain a single SV (e.g., Williams et al. 2015).

The approach presented in this chapter is analogous to the chemical toxicity distribution approach, except that UFs are applied to each effect concentration, prior to assembling the distribution. Our approach applies UFs tailored to study-specific information in individual CFED records, rather than applying a generic UF to distribution percentiles of the unadjusted effect concentrations.

A substantial number of SV point estimates were developed for each type of SV presented in this chapter. Total numbers of point estimates for population SV_{HIGH}, population SV_{LOW}, comprehensive SV_{HIGH} and comprehensive SV_{LOW} are 99, 167, 141, and 214, respectively. Complete lists of the point estimates and associated database information, by CEC, are provided in Attachment 4-2 for each type of SV.

There are at least two critical uses of the CEC SV point estimate distributions that are not provided by classical single-value SVs. The first use is to provide efficient and transparent illustration of the full breadth of possible values for a particular SV, which gives ecotoxicological context for mean SV values. Second, an SV point estimate distribution may be used as an empirical distribution for the toxicity assessment portion of a probabilistic ecological hazard assessment of CECs in fish.

For some CECs included in Section 4.4 (e.g., androstenedione, citalopram and lidocaine), there is very limited empirical fish toxicity information reported in the literature, such that their point estimate distributions are too sparse to be useful for the purposes mentioned above. In those cases, the probabilistic risk assessor may opt to develop modeled estimates of CEC effect concentrations for effect categories with limited or no empirical test information,

apply appropriate UFs (see Chapter 3) to modelled effect concentrations, and combine modelled SV point estimates with limited empirical data to populate the SV point estimate distribution. At this time, for the purpose of SV development, we neither recommend nor discourage the use of modelled estimates in the absence of sufficient empirical data. A review of the potential models, sources, and benefit-limitation analysis for obtaining modelled ecological effect concentrations is beyond the scope of this analysis.

4.3.3 CEC Effect-Specific SVs

Derivation

For each CEC, effect-specific SV_{HIGH} values, for both population-relevant and comprehensive type SVs, were developed as the geometric mean of corresponding effect-specific SV_{HIGH} point estimates (Figures 4-7 and 4-9; also see graphics for individual CECs in Section 4.4).

Effect-specific SV_{LOW} values were identified as the minimum value among SV_{LOW} point estimates in each Effect Category (Figures 4-8 and 4-10; also see graphics for individual CECs in Section 4.4).

Rationale

There is significant precedent in the ecotoxicological literature for deriving effect-specific SVs. Screening values derived from distributions of published effect concentrations for particular effect categories have been used in the development of SSDs and PNECs for aquatic hazard assessments of CECs. For instance, Capedieville et al. (2008) developed an SSD-based PNEC value for triclosan based on a distribution of NOECs and ECx values in aquatic organisms, but limited the effect endpoints to the survival, growth, and reproduction effect categories. Similarly, Caldwell et al. (2008) derived an SSD-based PNEC for 17α-ethinyl estradiol using only NOECs for reproductive effects in 26 aquatic species. In a follow-up analysis, Caldwell et al. (2012) updated the 17α-ethinyl estradiol PNEC and developed parallel SSD-based PNEC values for additional steroid estrogens - estrone, 17β-estradiol, and estriol - based on distributions of chronic NOECs for reproductive effects only. Caldwell et al. (2008, 2012) limited their PNEC derivations to reproductive effects based on prior information indicating that reproductive effects in fish were the most sensitive endpoints for estrogenic CECs.

No a priori assumptions were made concerning the most sensitive effect category for any of the CECs included in this report. Distributions of SV point estimates were developed as the basis for effect-specific SVs and mean SVs, rather than distributions of unadjusted effect concentrations (see Section 4.3.2). An SV point estimate distribution was developed for each effect category, for each CEC (Section 4.4). Effect-specific SVs were generated from those distributions.

Utility of CEC Effect-Specific SVs

Effect category-specific SVs are useful both for interpreting mean SVs, and for conducting custom hazard assessments for CEC impacts to fish. For each type of mean SV (population SV_{HIGH}, population SV_{LOW}, comprehensive SV_{HIGH}, and comprehensive SV_{LOW}), the mean values are computed as geometric means of the component Effect-specific SVs (see Tables 4-1a to 4-1d; Section 4.4). Inspection of the component Effect-Specific SVs for a given mean SV indicates which effect categories are the most important drivers of mean SV values, and clearly identifies datagaps in the published literature.

Effect-specific SVs may be applied in custom hazard assessments for receptor fish species that occupy different areas, and therefore may be exposed to different concentrations of CECs, during different parts of their life cycles. For instance, land-locked anadromous fish species in the Great Lakes are spawned, hatched, and occupy nursery habitats in stream systems, migrate to the lakes as subadults, and return to stream systems during subsequent breeding seasons as sexually mature adults. Hence, in a hazard assessment of CECs in a stream system used as salmonid spawning and nursery areas, the practitioner may elect to compare stream exposure concentrations to growth and developmental Effect-Specific SVs, which are most dramatic in early life stages and for which stream exposures would occur during early life stages. However, for adults, it may be more appropriate to use reproductive, mortality or behavioral Effect-specific SVs to assess hazard by comparing to long-term exposure concentrations in the lake, where adults spend the majority of their time.

4.3.4 CEC-Specific Mean SVs

Derivation

For each CEC, mean SV_{HIGH} and SV_{LOW} estimates were computed as:

Geometric mean of the Effect-Specific SVs / UF_{Data}.

Rationale

Development of paired mean SVs for each CEC provides for improved hazard scoring and robust interpretation of hazards to fish from surface water exposures to CECs. This approach combines the merits of lower bound and upper bound SVs, while reducing limitations of each in interpreting hazard. For instance, existing single-value lower bound SVs (see Table 1-1; e.g., Aquatic Life Benchmarks, PNECs) identify a concentration below which it is assumed there will be no effects, but indicate further study is necessary to determine degree of hazard if the exposure concentration is above that threshold. Existing upper-bound SVs (e.g., Aquatic Life Ambient Water Quality Criteria) indicate concentrations above which adverse impacts are expected, but provide no

information on sites or chemicals that may be removed from further investigation due to expected absence of impacts from contaminants under consideration. Application of the mean SV_{HIGH}/SV_{LOW} pair, derived from the CFED using consistent methodologies, provides both functions in one evaluation.

Comprehensive type mean SV pairs were derived using CEC-specific adverse effect concentrations, in all effect categories, using any adverse effect endpoint that is defined at the organism level of ecological organization and measured in individual fish. Population-relevant SV pairs were derived using only the population-relevant effect endpoints in survival, growth, reproductive, developmental, and behavioral effect categories. Further details on the distinction between comprehensive type and population-relevant effect endpoints are provided in Section 2.5 and Attachment 2-1.

Utility of CEC-Specific Mean SVs

Mean SVs are used in the familiar way to screen dissolved CEC concentrations in surface water for potential hazards to freshwater fish. Exposure concentrations are compared against each pair of SVs, for each CEC with screening values. Availability of both upper bound and lower bound mean SVs for each CEC allows for ordinal scoring of several categories of hazard, which can be assigned to each exposure concentration. For instance, exposures at concentrations greater than the SV_{HIGH} may be assigned a hazard score of, say 3, while exposure concentrations below the SV_{LOW} may be scored a value of 1, and concentrations that fall between the two SVs might be assigned a score of 2. For each CEC, uncertainty in assessment of potential hazard is greatest when exposure concentrations fall between the two SVs. Hence, in this example, confidence in hazard scores of 1 or 3 is higher than confidence in the intermediate score of 2. When hazard scores are averaged across detected CECs at each of several sampling sites, sites may be readily ranked with respect to hazard to fish due to CEC exposures.

Confidence in CEC-Specific Mean SVs

We provide an assessment of relative confidence in each CEC-specific mean SV estimate, based on quantity of ecotoxicological information in the CFED that was used to derive the estimates. Confidence levels are assigned based on three metrics of representation in the database:

- total number of Effect Categories represented by the set of available effect concentrations,
- number of represented Effect Categories with three or more SV point estimates, and
- number of fish species represented.

A rubric for assigning confidence levels based on these factors is provided in Table 4-3.

4.4 CEC Screening Values for Freshwater Fish

This section describes screening values for 14 CECs. A tabulated summary of mean and effect-specific SV estimates is provided in Tables 4-1a to 4-1d. Composite graphics for visual comparisons of Effect-specific SVs between CECs are provided in Figures 4-7 to 4-10.

Section 4.4 provides ecological risk practitioners and resource managers with an opportunity to examine the information used to derive each mean SV for each CEC, including:

- The breadth and depth of information currently available in the literature that was used to derive each SV;
- The range and distribution of derived SV point estimates that were the foundation for effect category-specific and mean SV values;
- An assessment of relative confidence in the estimated mean SVs for each CEC (Table 4-3); and
- Gaps in the knowledge base.

This information may be used by practitioners to determine which CECs to screen for potential impacts, and which SV(s) to apply for those CEC screenings, in a given hazard assessment.

A detailed description of SVs by CEC, and their ecotoxicological basis, is provided in the following 14 subsections. Information for each CEC is presented in subsections with increasing degrees of detail, including:

- Outline of CEC chemistry,
- Summary of SV numerical values (Mean, Effect-Specific , and Point Estimates),
- Description of the ecotoxicity database underpinning the SVs,
- Graphics illustrating relationships between the magnitude of SV point estimates and their paired cumulative uncertainty factors, and
- Graphics depicting the sequential derivation process for each SV for each CEC.

4.4.1 4-Androstene-3,17-dione

4.4.1.1 Chemical Summary

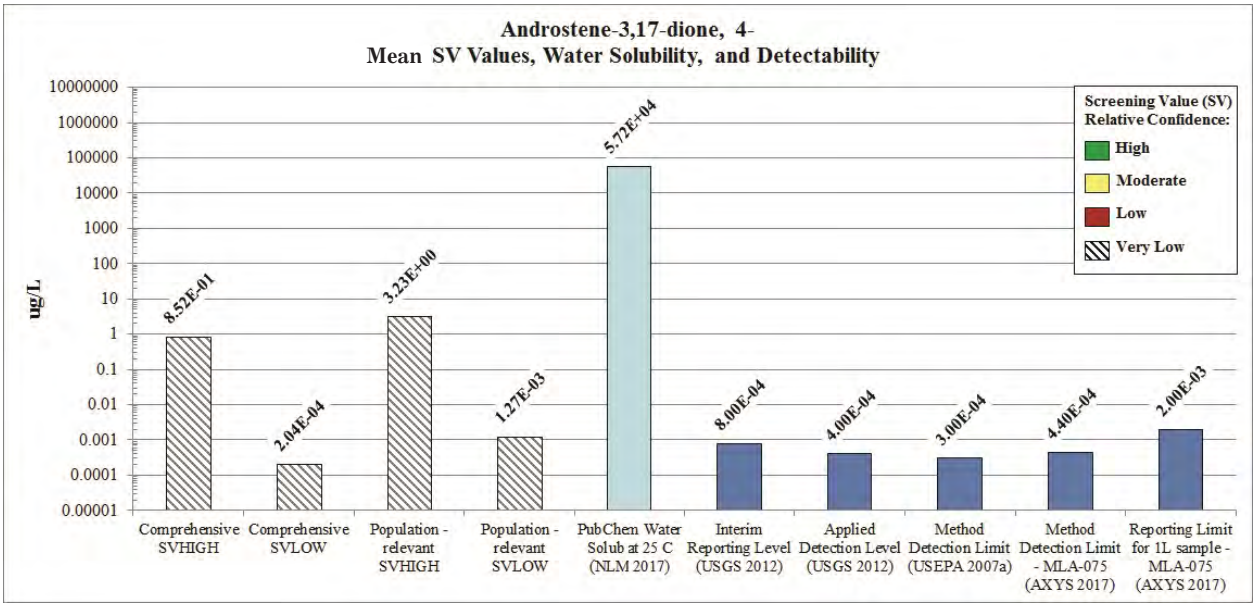
CEC Category: Hormone
CEC Subcategories: Therapeutic hormone

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Therapeutic androstenedione is a potent androgenic prohormone that is a direct precursor of testosterone and used as a supplement to increase plasma testosterone levels and muscle anabolism…. Androstenedione is a delta-4 19-carbon steroid that is produced not only in the testis, but also in the ovary and the adrenal cortex. Depending on the tissue type, androstenedione can serve as a precursor to testosterone as well as estrone and estradiol. It is the common precursor of male and female sex hormone."
- *CAS Number:* 63-05-8
- *Water Solubility:* 57.2 mg/L at 25 deg C
- *logKow:* 2.75
- *2010-2012 USGS Lab reporting Level (Choy et al. 2017): 0.0008 ug/L*
- *Interim Reporting Level - USGS Laboratory (USGS 2012): 0.0008 ug/L*
- *Applied Detection Level - USGS Techniques and Methods 5-B9 (USGS 2012): 0.0004 ug/L*
- *MDL - USEPA Method 1698 (USEPA 2007a): 0.0003 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.00044 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.002 ug/L*

4.4.1.2 Screening Value Summary

Mean SV Values (ug/L) for 4-Androstene-3,17-dione



Mean Population-relevant SV$_{HIGH}$ for 4-Androstene-3,17-dione: 3.23 μg/L

- *Relative Confidence:* Very Low. Sparse dataset. The literature provides effects information on only one effect category (Growth).
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Androstenedione (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: mosquitofish.
  - Life Stage(s): juvenile
  - Publication(s): Stanko and Angus 2007
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - Growth (1): standard length, weight gain
- *Cumulative Uncertainty Factor applied to the LOAEC for Androstenedione: 2.475 (see Attachment 4-2A for breakdown of component UF values)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Androstenedione:* 5

Mean Population-relevant SV$_{LOW}$ for 4-Androstene-3,17-dione: 0.00127 μg/L

- *Relative Confidence:* Very Low. Sparse dataset. Effects information from the literature is limited to only two Growth endpoints in juvenile mosquitofish and several Reproductive endpoints in adult guppies and juvenile mosquitofish.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Androstenedione (see Attachment 4-2B:*
  - *Population-relevant SV$_{LOW}$ Point Estimates)*
    - Species: mosquitofish, guppy
    - Life Stage(s): juvenile, adult
    - Publication(s): Hallgren and Olsen 2009, Stanko and Angus 2007
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
      - Growth (1): standard length, weight gain
      - Reproductive (2): gonopodium length, ovarian morphology and histology
- *Cumulative Uncertainty Factors applied to the three NOAECs to obtain Population-relevant SV$_{LOW}$ point estimates for Androstenedione:* two $UF_{\prod\text{-}Low}$ = 157.2; one $UF_{\prod\text{-}Low}$ = 314.5 *(see Attachment 4-2B for breakdown of the component UF values)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$values for Androstenedione:* 2

Mean Comprehensive SV$_{HIGH}$ for 4-Androstene-3,17-dione: 0.852 µg/L

- *Relative Confidence:* Very Low. Sparse dataset. The literature provides effects information on only one effect category (Growth).
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Androstenedione (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: mosquitofish, guppy
  - Life Stages: juvenile, adult
  - Publication(s): Hallgren and Olsen 2009, Stanko and Angus 2007
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - Growth (1): standard length, weight gain
    - Reproductive (2): gonopodium length, ovarian morphology and histology
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for 4-Androstene-3,17-dione: ranged from 2.6 to 5.3 (see Attachment 4-2C for breakdown of omponent UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for 4-Androstene-3,17-dione:* 5

Mean Comprehensive SV$_{LOW}$ for 4-Androstene-3,17-dione: 0.000204 µg/L

- *Relative Confidence:* Very Low. Sparse dataset. Effects information from the literature is limited to only two Growth endpoints in juvenile mosquitofish and several Reproductive endpoints in adult guppies and juvenile mosquitofish.
- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Androstenedione (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: mosquitofish, guppy
  - Life Stage(s): juvenile, adult
  - Publication(s): Hallgren and Olsen 2009, Stanko and Angus 2007
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - Growth (1): standard length, weight gain
    - Reproductive (2): gonopodium length, ovarian morphology and histology
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Androstenedione:* ranged from 392 to 783 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect- Specific SV$_{LOW}$ values for Androstenedione:* 5

Effect Category-Specific SV Values (ug/L) for 4-Androstene-3,17-dione

Population-relevant SV_{HIGH}: Only the Growth effect category is represented with an effect-specific SV of 16.2 ug/L, based on only one SV point estimate.

Population-relevant SV_{LOW}: Growth and Reproductive effect-specific SVs were 0.0254 and 0.000254 ug/L, based on only one and two SV point estimates, respectively.

Comprehensive SV_{HIGH} : Growth and Reproductive effect-specific SVs were 15.2 and 1.2 ug/L, based on only one and two SV point estimates, respectively.

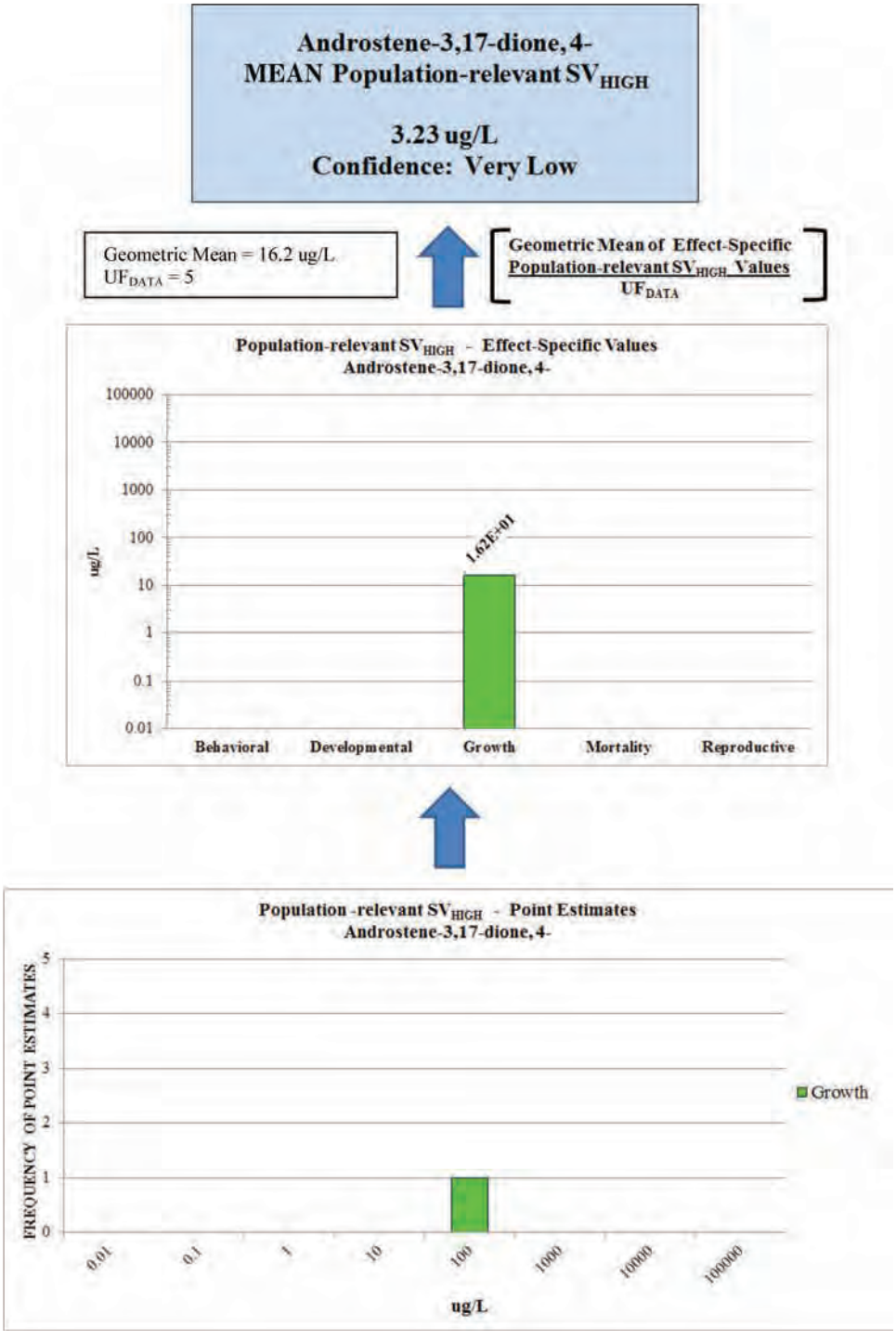
Comprehensive SV_{LOW} : Growth and Reproductive effect-specific SVs were 0.0102 and 0.000102 ug/L, based on only one and two SV point estimates, respectively.

SV Point Estimates for 4-Androstene-3,17-dione

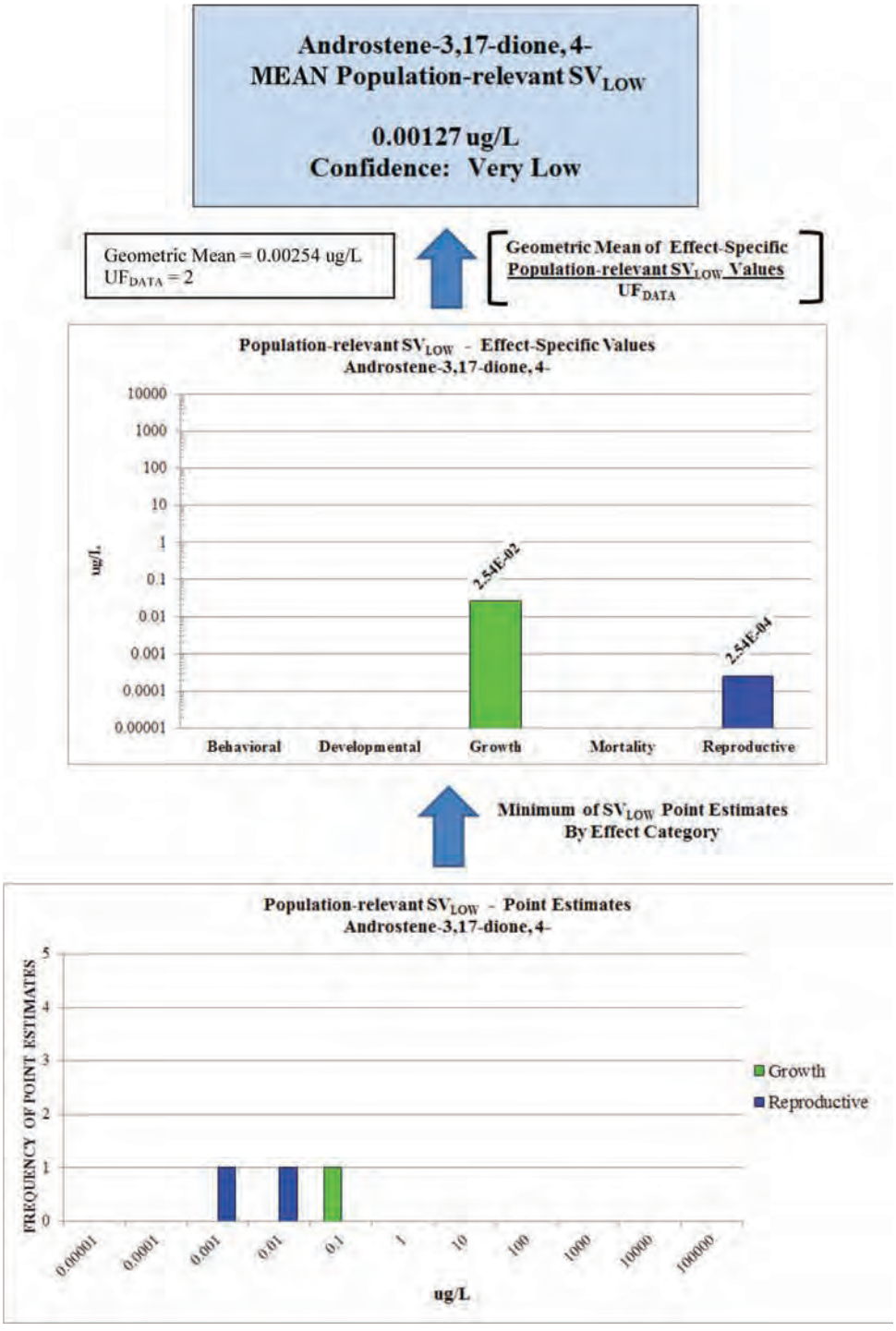
Effect Category	4-Androstene-3,17-dione Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral				
Developmental				
Growth	16.2 (1)	0.0254 (1)	15.2 (1)	0.0102 (1)
Mortality				
Reproductive		0.000254 – 0.00223 (2)	0.152 – 9.47 (2)	0.000102 (2)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.1.3 SV Development: Graphics for 4-Androstene-3,17-dione

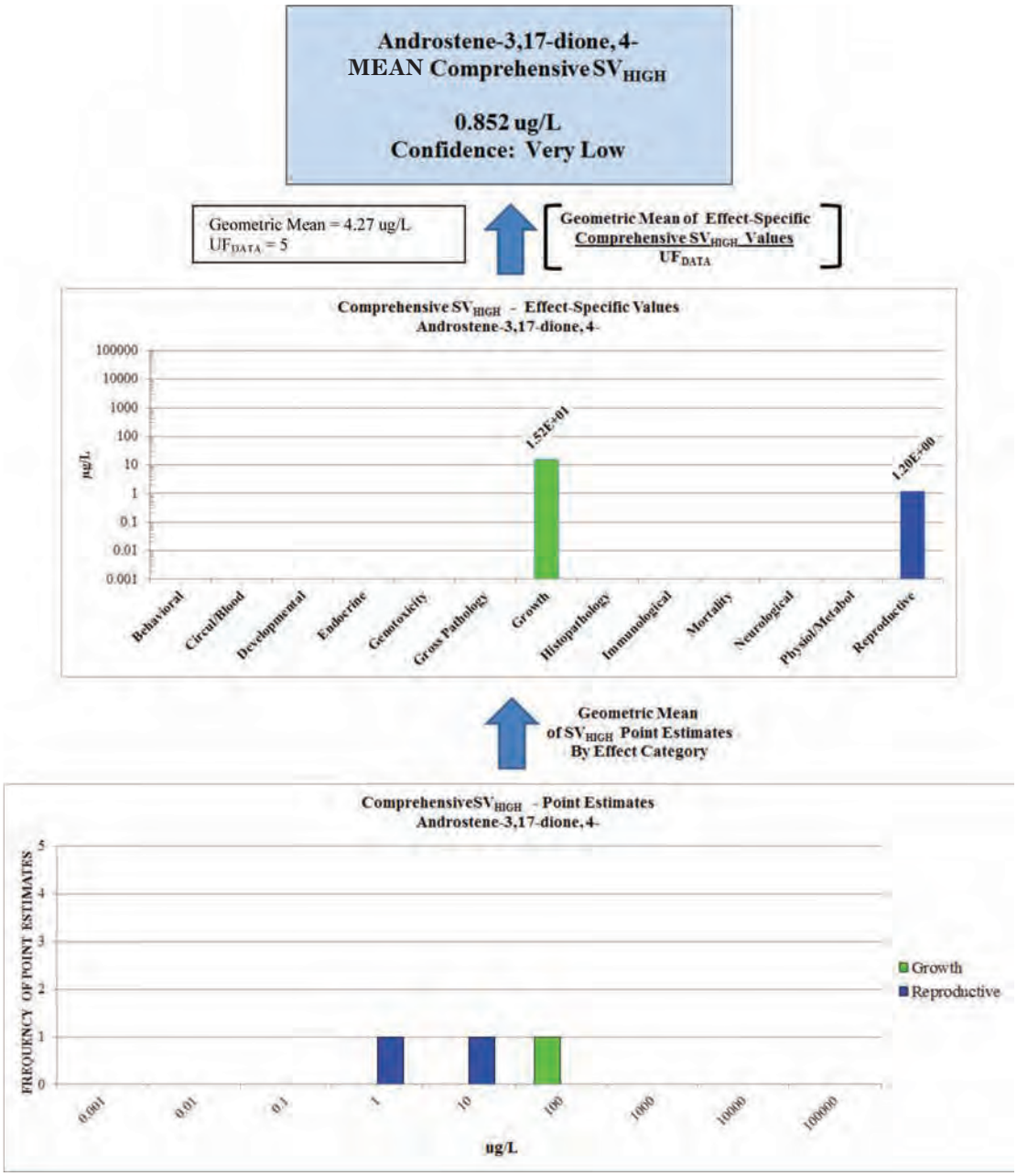
Population-relevant SV_{HIGH} Values for 4-Androstene-3,17-dione: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



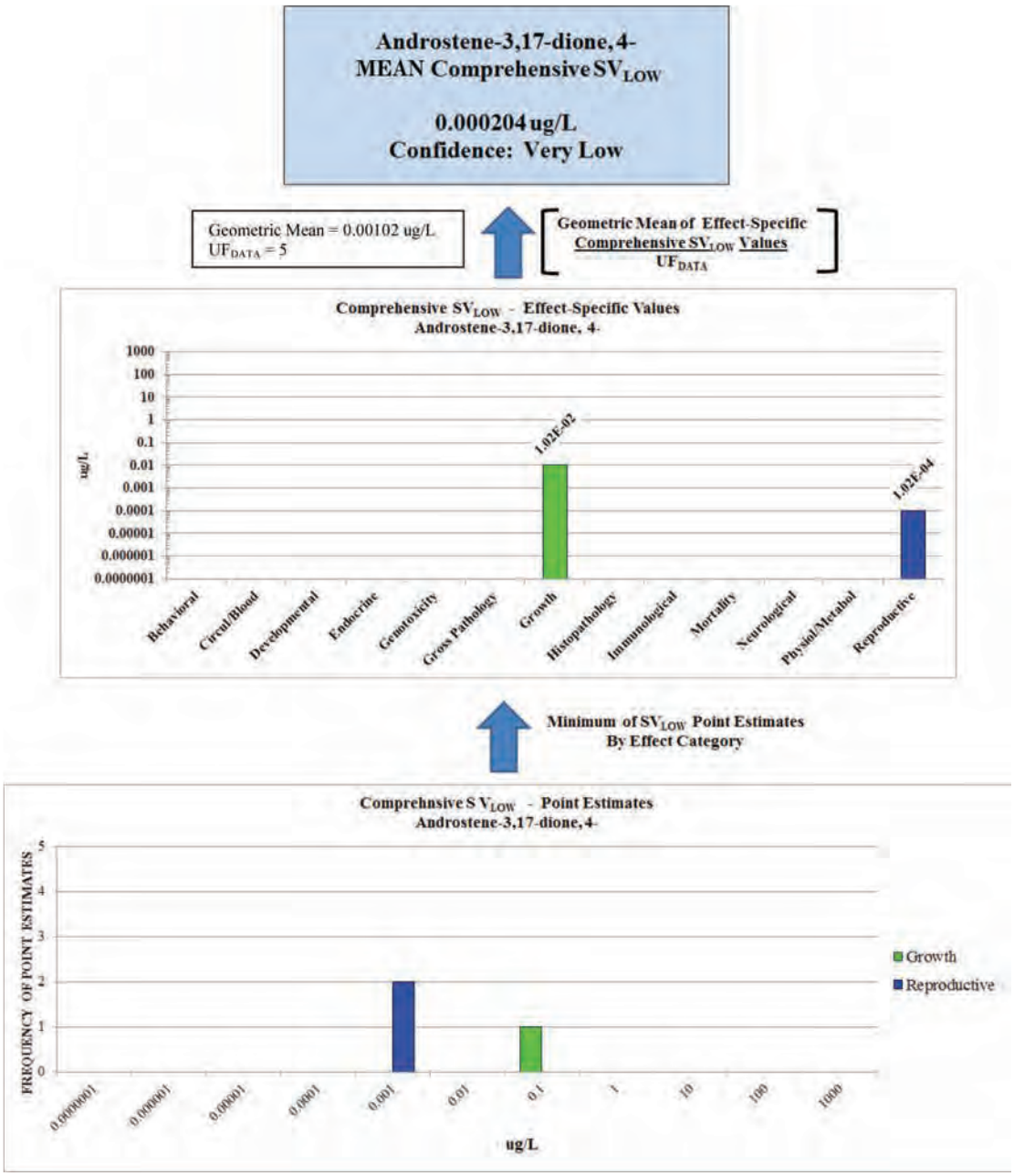
Population-relevant SV_{LOW} Values for 4-Androstene-3,17-dione: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{HIGH} Values for 4-Androstene-3,17-dione: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for 4-Androstene-3,17-dione: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



4.4.2 Bisphenol A

4.4.2.1 Chemical Summary

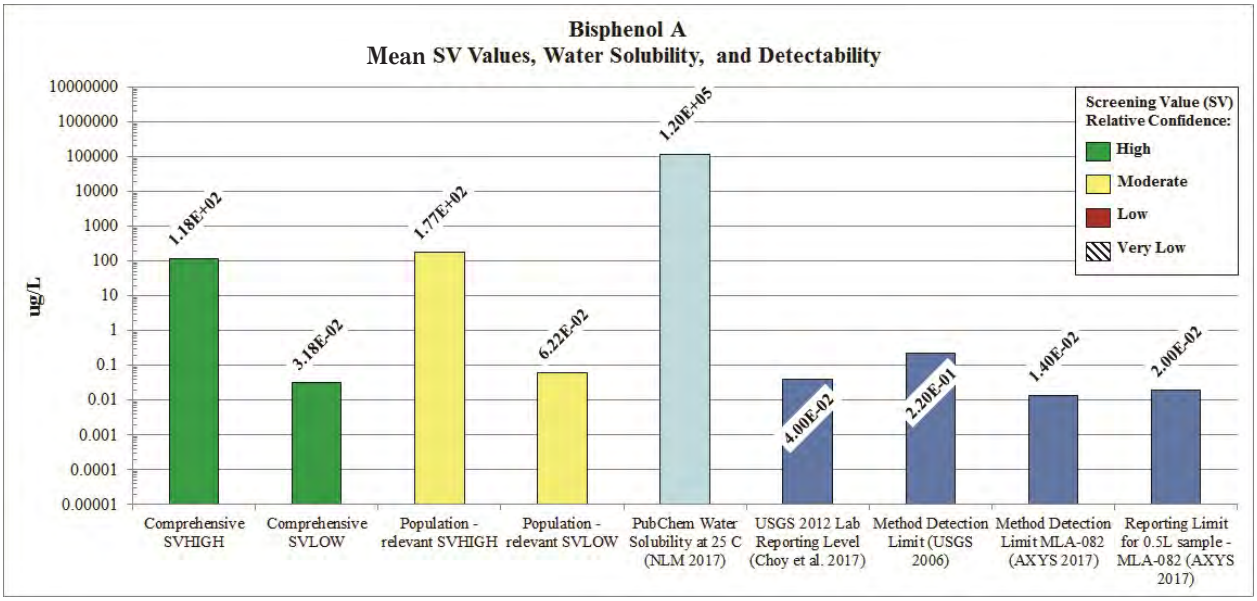
CEC Category: Plasticizer

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "Bisphenol A, commonly abbreviated as BPA, is an organic compound with two phenol functional groups. It is a difunctional building block of several important plastics and plastic additives. With an annual production of 2–3 million metric tonnes, it is an important monomer in the production of polycarbonate. It is a potential food contaminant arising from its use in reusable polycarbonate food containers such as water carboys, baby bottles and kitchen utensils."
- *CAS Number:* 80-05-7
- *Water Solubility:* 120 mg/L at 25 deg C
- *logKow:* 3.32
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.04 ug/L*
- *MDL – USGS Techniques and Methods 5-B4 (USGS 2006): 0.22 ug/L*
- *MDL – AXYS Method MLA-082 (AXYS 2017): 0.014 ug/L*
- *Reporting Limit for 0.5L sample – AXYS Method MLA-082 (AXYS 2017): 0.002 ug/L*

4.4.2.2 Screening Value Summary

Mean SV Values (ug/L) for Bisphenol A



Mean Population-relevant SV$_{HIGH}$ for Bisphenol A: 177 μg/L

- *Relative Confidence:* High. Applicable literature information was compiled for all five population-relevant effect categories. Robust datasets include effects data on five fish species and all four life stages for the Developmental category and effects in nine species for the Reproductive category.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Bisphenol A (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
    - Species: Atlantic salmon, brown trout, fathead minnow, goldfish, guppy, Japanese medaka, ricefish, swordtail, zebrafish.
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): 24 separate studies published between 2000 and 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
        - Behavioral (1): mating behavior
        - Developmental (18): oxidative stress, hatching rates, hatch timing, survival (parental, embryo, larval), spinal curvature, yolk sac edema, heart inflammation, heart rate, organ development, apoptosis, DNA damage, neuron axonal growth, other structural anomalies, embryo and larval length and weight, sex ratio, fecundity and egg fertilization in subsequent generations, development rate, edema, hemorrhage, histopathology in gonads, kidney, heart, liver, and thyroid
        - Growth (1): length and weight
        - Mortality (2)
        - Reproductive (11): sperm motility and velocity, reproductive hormone levels, intersex, fertility, eggs per female, hatchability, number spawns per breeding pair, GSI, ovulation timing, testis morphology, gonad histopathology, sperm count, sperm length, sperm total mass, sperm density, % viable sperm, spermatogenesis, oogenesis
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population- relevant SV$_{HIGH}$ point estimates for Bisphenol A: ranged from* 2.5 to 7.4 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Bisphenol A:* 1

Mean Population-relevant SV$_{LOW}$ for Bisphenol A: 0.0622 μg/L

- *Relative Confidence:* High. Applicable literature information was compiled for all five population-relevant effect categories. Robust datasets include effects data on six fish species and all four life stages for the Developmental category and effects data in eight species for the Reproductive category.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Bisphenol A (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
    - Species: Atlantic salmon, brown trout, common carp fathead minnow, goldfish, guppy, Japanese medaka, rare minnow, ricefish, swordtail, zebrafish.
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): 28 separate studies published between 2000 and 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
        - Behavioral (1): mating behavior
        - Developmental (23): oxidative stress, hatching rates, hatch and swim-up timing, survival (parental, embryo, larval), sexual maturation, spinal curvature, yolk sac edema, heart inflammation, heart rate, organ development, apoptosis, DNA damage, neuron axonal growth, other structural anomalies, embryo and larval length and weight, sex ratio, fecundity, egg viability and egg fertilization in subsequent generations, development rate, edema, hemorrhage, histopathology in gonads, kidney,

heart, liver, and thyroid
- Growth (8): length and weight
- Mortality (7)
- Reproductive (13): sperm motility and velocity, reproductive hormone levels, intersex, fertility, eggs per female, hatchability, number spawns per breeding pair, GSI, ovulation timing, testis morphology, gonad histopathology, sperm count, sperm length, sperm total mass, sperm density, % viable sperm, spermatogenesis, oogenesis, ovary development, egg morphology

o *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SVLOW point estimates for Bisphenol A*: ranged from 78.6 to 1179 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Population-relevant SVLOW value from Effect-Specific SVLOW values for Bisphenol A:* 1

Mean Comprehensive SVHIGH for Bisphenol A: 118 μg/L

o *Relative Confidence:* Moderate. Relevant information concerning six of the 13 effect categories was compiled from the literature, but exposure and endpoint representation was sparse for four of them.

o *Representation in the Comprehensive SVHIGH Dataset for Bisphenol A (see Attachment 4-2C: Comprehensive SVHIGH Point Estimates)*

- Species: Atlantic salmon, brown trout, common carp, fathead minnow, goldfish, guppy, Japanese medaka, rare minnow, ricefish, swordtail, zebrafish.
- Life Stage(s): embryo, larva, juvenile, adult
- Publication(s): 29 separate studies published between 2000 and 2014
- Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study.
  - Behavioral (1): mating behavior
  - Developmental (20): oxidative stress, immune response gene expression, thyroid hormone regulation, hatching rates, hatch timing, survivalparental, embryo, larval), spinal curvature, yolk sac edema, heart inflammation, heart rate, organ development, apoptosis, DNA damage, neuron axonal growth, other structural anomalies, embryo and larval length and weight, sex ratio, fecundity and egg fertilization in subsequent generations, development rate, edema, hemorrhage, histopathology in gonads, kidney, heart, liver, and thyroid
  - Gross Pathology (1): kidney size changes related to histopathologies
  - Growth (1): length and weight
  - Mortality (2)
  - Reproductive (15): sperm motility and velocity, reproductive hormone levels, plasma vitellogenin, intersex, fertility, eggs per female, hatchability, number spawns per breeding pair, GSI, ovulation timing, gonad morphology and weights, gonad histopathology, sperm count, sperm length, sperm total mass, sperm density, % viable sperm, spermatogenesis, oogenesis

o *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SVHIGH point estimates for Bisphenol A:* ranged from 2.64 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SVHIGH value from Effect-Specific SVHIGH values for Bisphenol A:* 1

Mean Comprehensive SVLOW for Bisphenol A: 0.0318 μg/L

o *Relative Confidence:* Moderate. Relevant information concerning six of the 13 effect categories was compiled from the literature, but exposure and endpoint representation was sparse for two of them.

o *Representation in the Comprehensive SVLOW Dataset for Bisphenol A (see Attachment 4-2D: Comprehensive SVLOW Point Estimates)*

- Species: Atlantic salmon, brown trout, common carp, fathead minnow, goldfish, guppy, Japanese medaka, rare minnow, ricefish, swordtail, zebrafish.
- Life Stage(s): embryo, larva, juvenile, adult
- Publication(s): 30 separate studies published between 2000 and 2014
- Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
  - Behavioral (1): mating behavior
  - Developmental (26): oxidative stress, immune response gene expression, thyroid hormone regulation,

hypothalamic-pituitary-thyroid axis hormone expression, hatching rates, hatch and swim-up timing, survival (parental, embryo, larval), sexual maturation, spinal curvature, yolk sac edema, heart inflammation, heart rate, organ development, apoptosis, DNA damage, neuron axonal growth, other structural anomalies, embryo and larval length and weight, sex ratio, fecundity, egg viability and egg fertilization in subsequent generations, development rate, edema, hemorrhage, histopathology in gonads, kidney, heart, liver, and thyroid

- Gross Pathology (2): kidney size changes related to histopathologies, other gross lesions, body coloration
- Growth (8): length and weight
- Mortality (7)
- Reproductive (15): sperm motility and velocity, reproductive hormone levels, intersex, fertility, eggs per female, hatchability, number spawns per breeding pair, GSI, ovulation timing, testis morphology, gonad histopathology, sperm count, sperm length, gamete total mass, sperm density, % viable sperm, spermatogenesis, oogenesis, ovary development, egg morphology

o *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Bisphenol A:* ranged from 196 to 2937 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Bisphenol A:* 1

Effect Category-Specific SV Values (ug/L) for Bisphenol A

Population-relevant SV_{HIGH}: Data on bisphenol A were sufficient to estimate SVs for each of the five population-relevant effect categories (Table 4-1a). Effect-specific Population SV_{HIGH} values range from 18.3 ug/L (Reproductive) to 68 ug/L (Mortality).

Population-relevant SV_{LOW} : Data were sufficient to estimate SVs for each of the five population-relevant effect categories (Table 4-1b). Effect-specific Population SV_{LOW} values range from 0.000636 ug/L (Developmental) to 3.82 ug/L (Behavioral).

Comprehensive SV_{HIGH} : Data were sufficient to estimate SVs for six of the 13 effect categories (Table 4-1c). Effect-specific Comprehensive SV_{HIGH} values range from 10.4 ug/L (Reproductive) to 638 ug/L (Mortality).

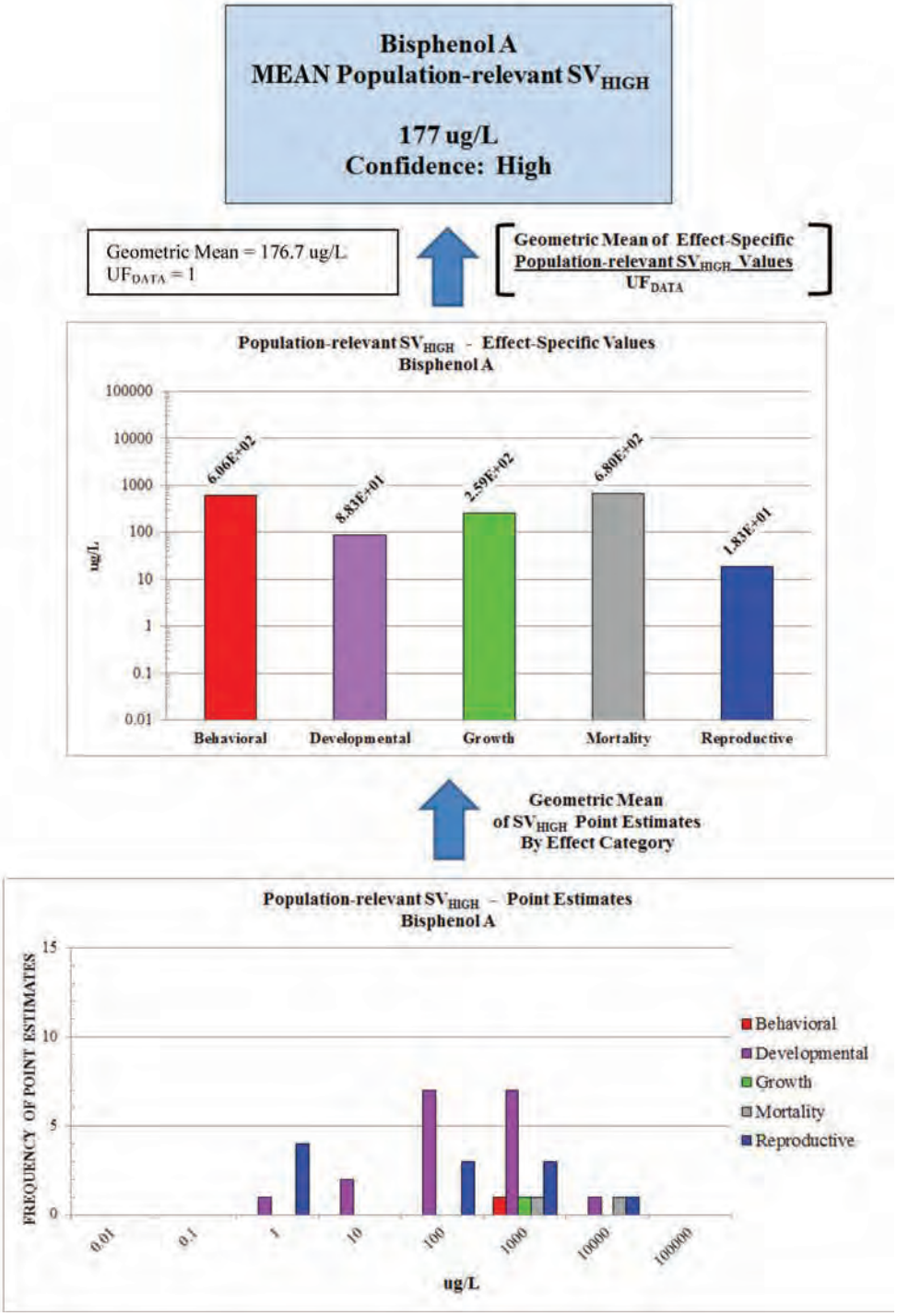
Comprehensive SV_{LOW} : Data were sufficient to estimate SVs for six of the 13 effect categories (Table 4-1d). Effect-specific Comprehensive SV_{LOW} values range from 0.000102 ug/L (Developmental) to 1.53 ug/L (Behavioral).

SV Point Estimates for Bisphenol A

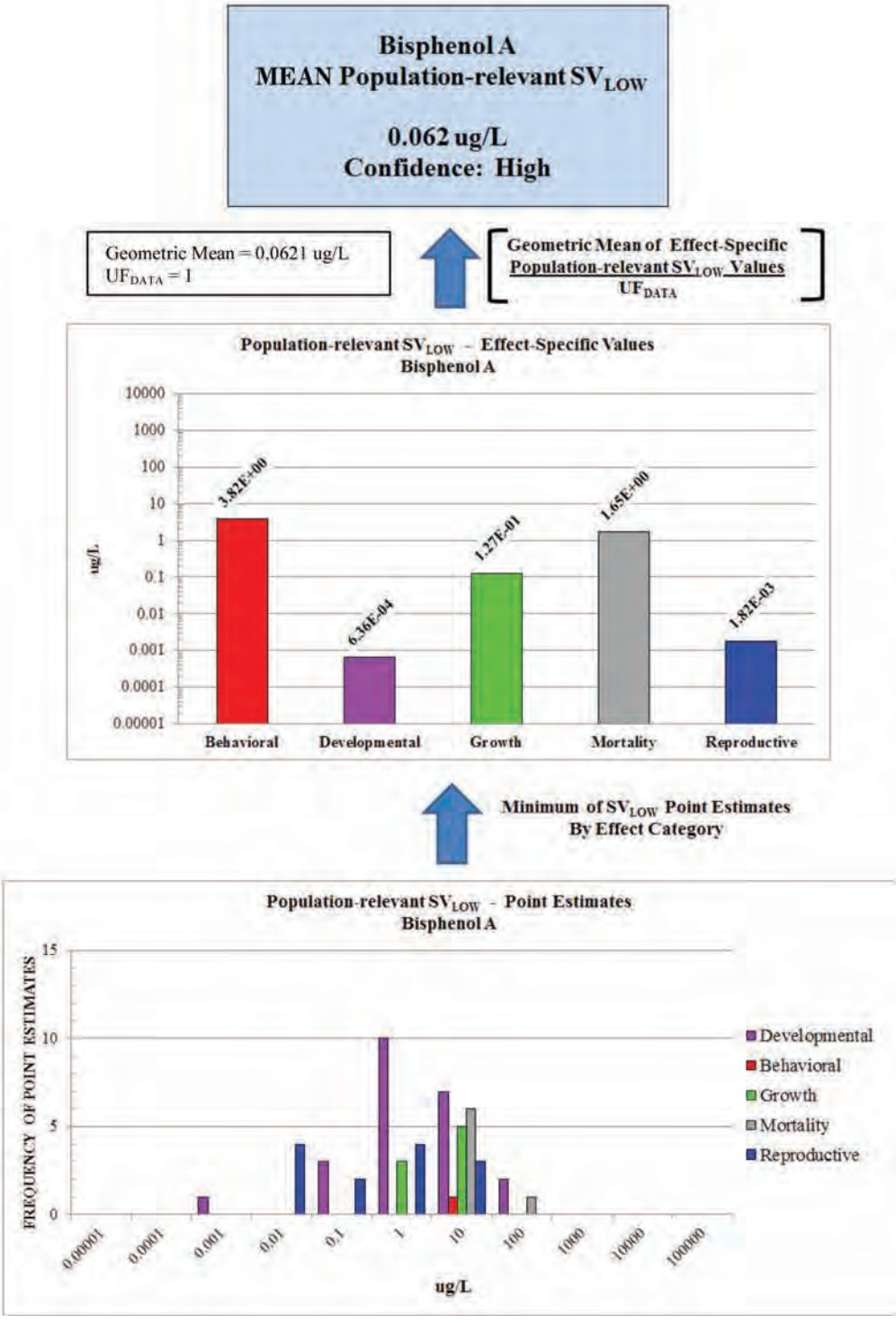
Effect Category	Bisphenol A Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	606 (1)	3.8 (1)	568 (1)	1.5 (1)
Developmental	0.404 – 2436 (18)	0.00064 – 25.6 (23)	0.038 – 2284 (20)	0.000102 – 10.3 (26)
Growth	259 (1)	0.127 – 8.14 (8)	242 (1)	0.051 – 3.27 (8)
Mortality	229 – 2020 (2)	1.65 – 19.8 (7)	214 – 1894 (2)	0.66 – 8.0 (7)
Reproductive	0.17 – 2020 (11)	0.0018 – 3.18 (13)	0.16 – 1894 (15)	0.00072 – 1.28 (15)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology			49.2 (1)	0.27 – 8.0 (2)
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.2.3. SV Development: Graphics for Bisphenol A

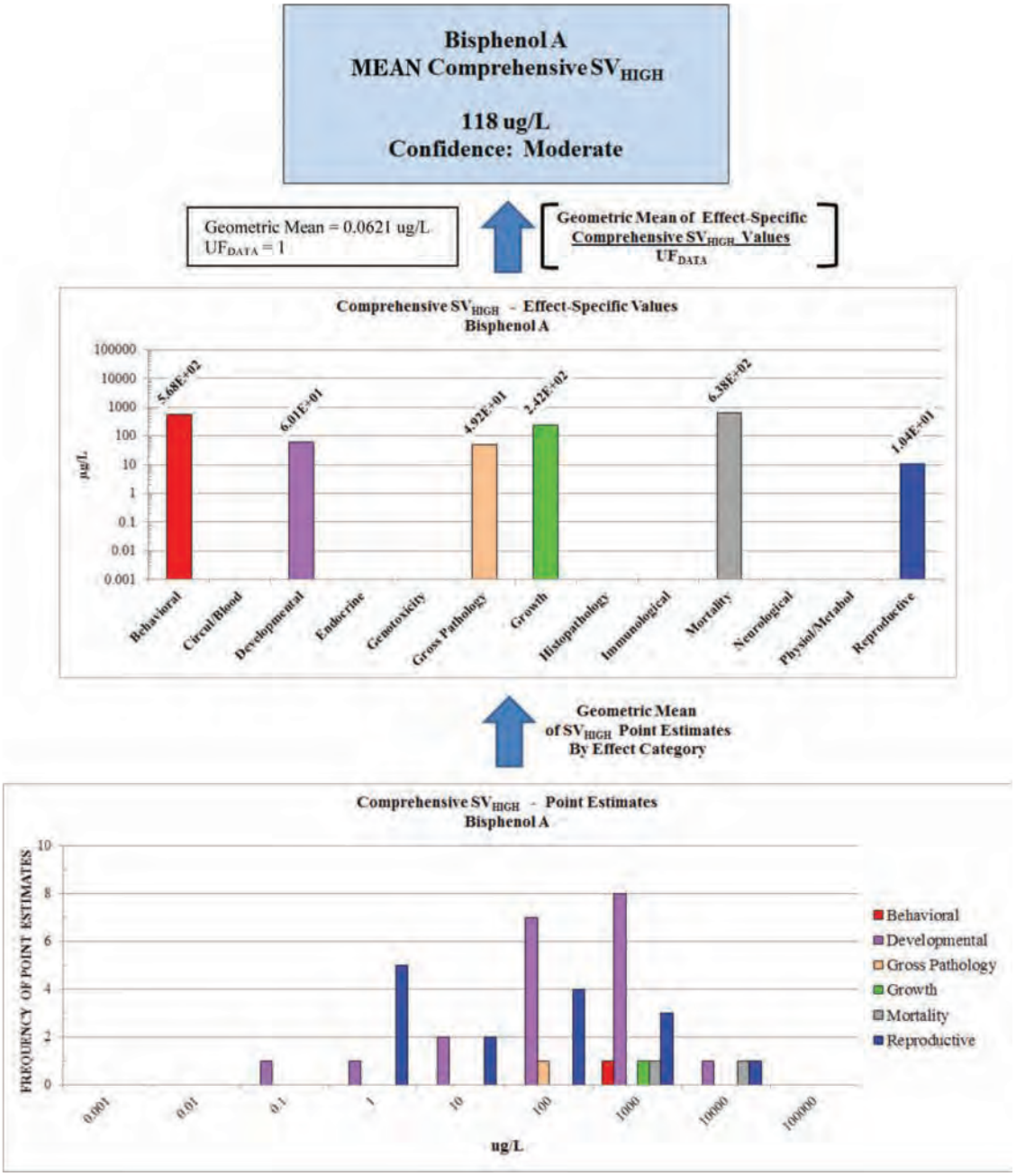
Population-relevant SV_{HIGH} Values for Bisphenol A: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



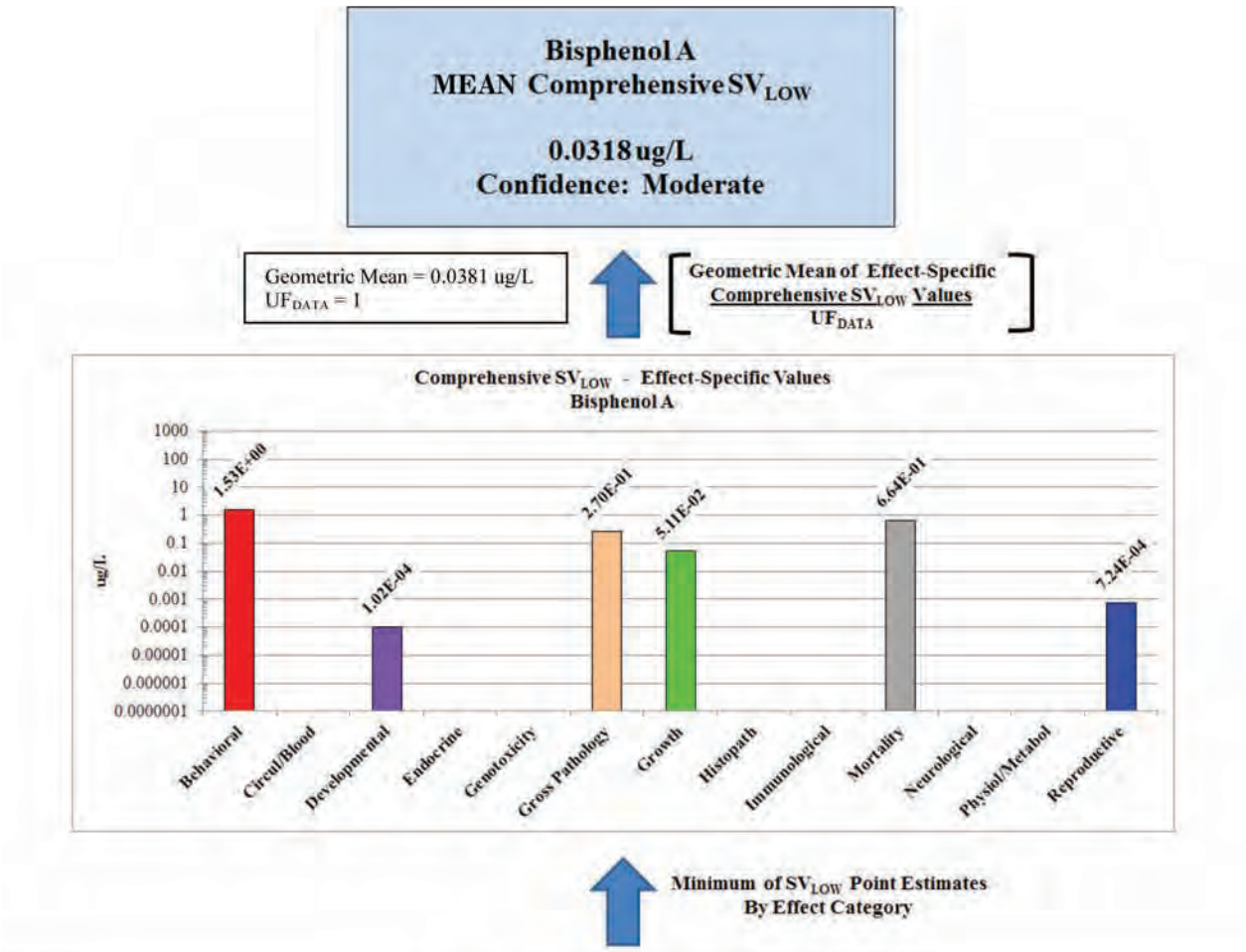
Population-relevant SV_{LOW} Values for Bisphenol A: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

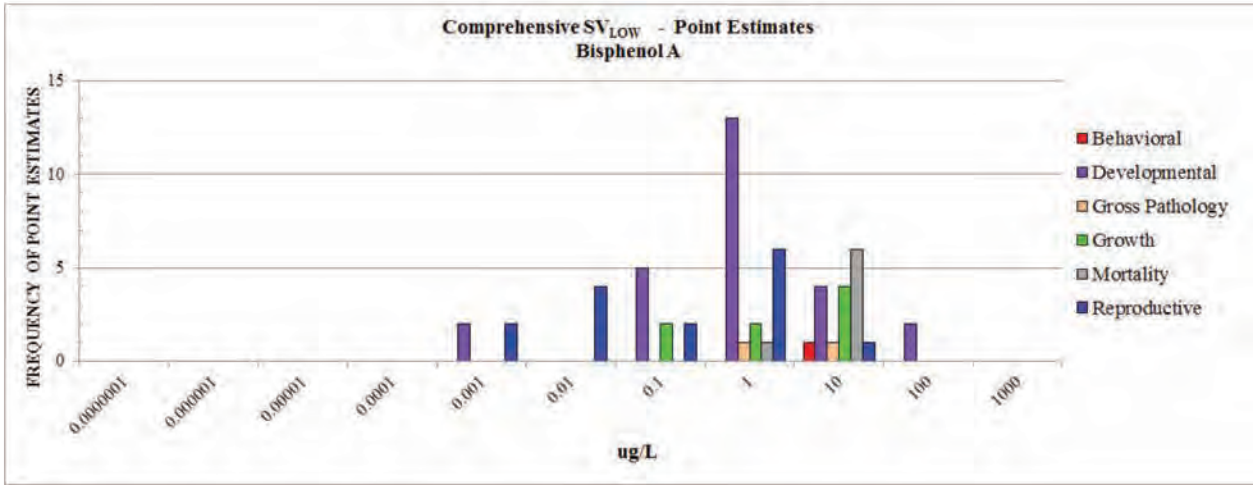


Comprehensive SV_{HIGH} Values for Bisphenol A: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Bisphenol A: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.3 Carbamazepine

4.4.3.1 Chemical Summary

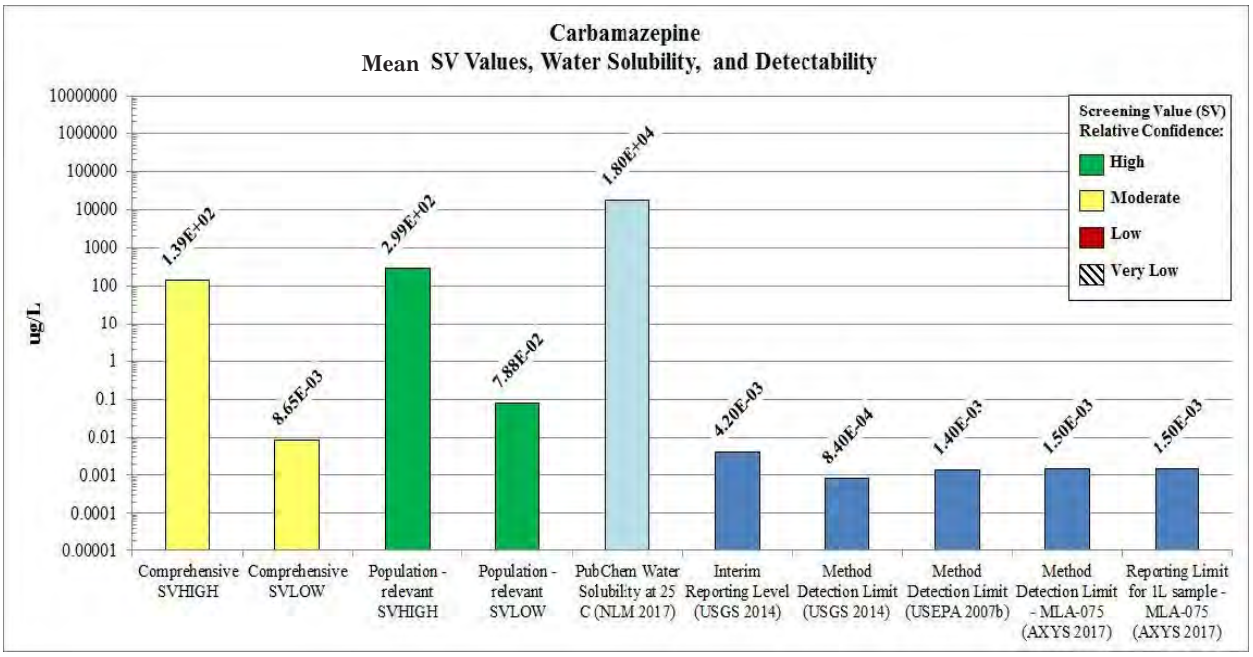
CEC Category: Pharmaceutical
CEC Subcategory: Anticonvulsant

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "Carbamazepine is a tricyclic compound chemically related to tricyclic antidepressants (TCA) with anticonvulsant and analgesic properties. Carbamazepine exerts its anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation. Its analgesic activity is not understood; however, carbamazepine is commonly used to treat pain associated with trigeminal neuralgia."
- *CAS Number:* 298-46-4
- *Water Solubility:* 18 mg/L at 25 deg C
- *logKow:* 2.45
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 0.16 ug/L*
- *Interim Reporting Level - USGS Laboratory (USGS 2014): 0.0042 ug/L*
- *MDL – USGS Techniques and Methods 5-B10 (USGS 2014): 0.00084 ug/L*
- *MDL - USEPA Method 1694 (USEPA 2007b): 0.0014 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0015 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.0015 ug/L*

4.4.3.2 Screening Value Summary

Mean SV Values (ug/L) for Carbamazepine



Mean Population-relevant SV$_{HIGH}$ for Carbamazepine: 299 μg/L

- *Relative Confidence:* High. Although literature information was compiled for all five population-relevant effect categories, none of the effect-specific datasets was robust. Three of the categories had few SV point estimates. Behavioral and Developmental categories each had a number of SV point estimates, but fish species representation was limited to zebrafish, only, in the Developmental category.

- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Carbamazepine (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, pumpkinseed, rainbow trout, zebrafish.
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 12 separate studies published between 2009 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Behavioral(6): courtship behavior, startle response, light-dark preference, feeding duration, swimming speed, larval activity and swimming velocity
    - Developmental (5): hatch rate, embryo mortality, deformations of spinal cord, head, otolith, and tail, pericardial edema, yolk sac edema, growth, heart deformation, heart rate, dorsal curvature, hemorrhages, tail length, egg production, liver, kidney and gonad histology, pigmentation, sperm morphology and speed in subsequent generations
    - Growth (1): condition factor
    - Mortality (1)
    - Reproductive (2): GSI, embryo production, sperm density, spermatogenesis, oogenesis, gonad morphology and histopathology, reproductive hormone levels

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Carbamazepine:* ranged from 2.5 to 7.4 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Carbamazepine:* 1

Mean Population-relevant SV$_{LOW}$ for Carbamazepine: 0.0788 μg/L

- *Relative Confidence:* High. Although literature information was compiled for all five population-relevant effect categories, none of the effect-specific datasets is robust. SV point estimates in three of the categories are sparse.

- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Carbamazepine (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, pumpkinseed, rainbow trout, zebrafish.
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 14 separate studies published between 2009 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Behavioral (6): courtship behavior, startle response, light-dark preference, feeding duration, swimming speed, larval activity and swimming velocity
    - Developmental (6): hatch rate, hatching success, embryo mortality, prevalence of embryos with defects, deformations of spinal cord, head, otolith, and tail, pericardial edema, yolk sac edema, embryo and larval growth, heart deformation, heart rate, dorsal curvature, hemorrhages, tail length, egg production, liver, kidney and gonad histology, pigmentation, sperm morphology and speed in subsequent generations
    - Growth (3): condition factor, body length, fork length, weight
    - Mortality (2)
    - Reproductive (2): GSI, embryo production, sperm density, spermatogenesis, oogenesis, gonad morphology and histopathology, reproductive hormone levels

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SVLOW point estimates for Carbamazepine:* ranged from 78.6 to 786 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Population-relevant SVLOW value from Effect-Specific SVLOW values for Carbamazepine:* 1

Mean Comprehensive SVHIGH for Carbamazepine: 139 μg/L

- *Relative Confidence:* Moderate. While nine of the 13 effect categories are represented, six of these categories have few observations.

- *Representation in the Comprehensive SVHIGH Dataset for Carbamazepine (see Attachment 4-2C: Comprehensive SVHIGH Point Estimates)*

    - Species: common carp, fathead minnow, Japanese medaka, pumpkinseed, rainbow trout, zebrafish.
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): 14 separate studies published between 2007 and 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
        - Behavioral (6): courtship behavior, startle response, light-dark preference, feeding duration, swimming speed, larval activity and swimming velocity
        - Circulatory/Blood Constituents (2): hematological parameters, leukocyte differential counts, blood plasma chemistry
        - Developmental (5): hatch rate, embryo mortality, deformations of spinal cord, head, otolith, and tail, pericardial edema, yolk sac edema, growth, heart deformation, heart rate, dorsal curvature, hemorrhages, tail length, egg production, liver, kidney and gonad histology, pigmentation, sperm morphology and speed in subsequent generations
        - Growth (1): condition factor
        - Histopathology (2): multiple histopathologic endpoints in kidneys, gills, liver
        - Mortality (1)
        - Neurological (2): oxidative damage in brain
        - Physiological/Metabolism (4): oxidative stress indicators, enzyme activities related to oxidative stress, energy metabolism, and osmoregulation
        - Reproductive (2): GSI, embryo production, sperm density, spermatogenesis, oogenesis, gonad morphology and histopathology, reproductive hormone levels

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SVHIGH point estimates for Carbamazepine:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Comprehensive SVHIGH value from Effect-Specific SVHIGH values for Carbamazepine:* 1

Mean Comprehensive SVLOW for Carbamazepine: 0.00865 μg/L

- *Relative Confidence:* Moderate. While nine of the 13 effect categories are represented, five of these datasets have few observations.

- *Representation in the Comprehensive SVLOW Dataset for Carbamazepine (see Attachment 4-2D: Comprehensive SVLOW Point Estimates)*

    - Species: common carp, fathead minnow, Japanese medaka, pumpkinseed, rainbow trout, zebrafish.
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): 16 separate studies published between 2007 and 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
        - Behavioral (7): courtship behavior, startle response, light-dark preference, feeding duration, swimming speed, larval activity and swimming velocity
        - Circulatory/Blood Constituents (2): hematological parameters, leukocyte differential counts, blood plasma chemistry
        - Developmental (6): hatch rate, hatching success, embryo mortality, prevalence of embryos with defects, deformations of spinal cord, head, otolith, and tail, pericardial edema, yolk sac edema, embryo and larval growth, heart deformation, heart rate, dorsal curvature, hemorrhages, tail

length, egg production, liver, kidney and gonad histology, pigmentation, sperm morphology and speed in subsequent generations
- Growth (3): condition factor, body length, fork length, weight
- Histopathology (2): multiple histopathologic endpoints in kidneys, gills, liver
- Mortality (2)
- Neurological (2): oxidative damage in brain
- Physiological/Metabolism (4): oxidative stress indicators, enzyme activities related to oxidative stress, energy metabolism, and osmoregulation
- Reproductive (2): GSI, embryo production, sperm density, spermatogenesis, oogenesis, gonad morphology and histopathology, reproductive hormone levels

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SVLOW point estimates for Carbamazepine:* ranged from 196 to 2937 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SVLOW value from Effect-Specific SVLOW values for Carbamazepine:* 1

Effect Category-Specific SV Values (ug/L) for Carbamazepine

Population-relevant SV_{HIGH}: Data on carbamazepine were sufficient to estimate SVs for each of the five population-relevant effect categories (Table 4-1a). Effect-specific Population SV_{HIGH} values range from 852 ug/L (Reproductive) to 1,330 ug/L (Mortality).

Population-relevant SV_{LOW} : Data were sufficient to estimate SVs for each of the five population-relevant effect categories (Table 4-1b). Effect-specific Population SV_{LOW} values range from 0.00127 ug/L (Reproductive) to 5.66 ug/L (Mortality).

Comprehensive SV_{HIGH} : Data were sufficient to estimate SVs for nine of the 13 effect categories (Table 4-1c). Effect-specific comprehensive SV_{HIGH} values range from 0.189 ug/L (Histopathology) to 1,250 ug/L (Mortality).

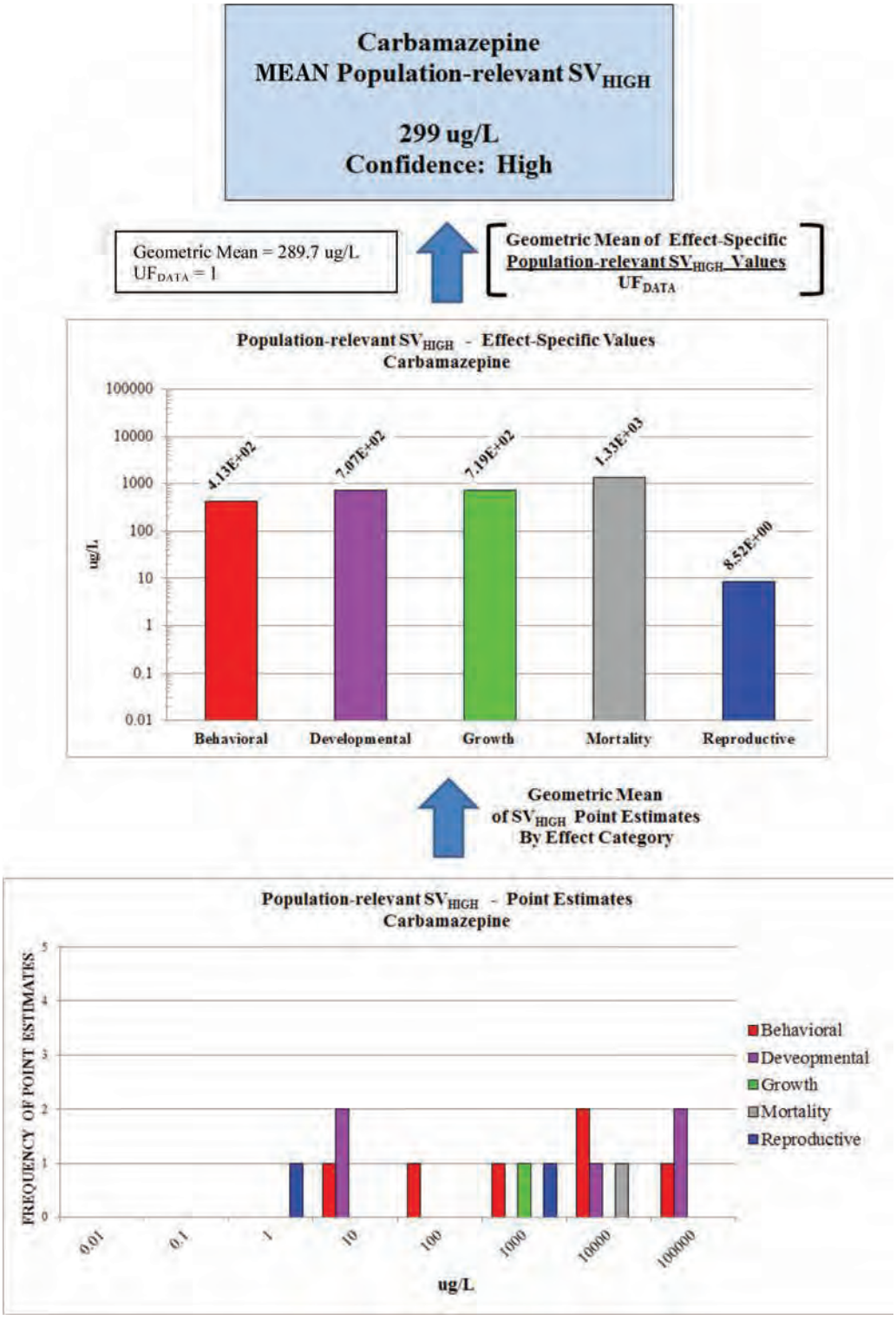
Comprehensive SV_{LOW} : Data were sufficient to estimate SVs for nine of the 13 effect categories (Table 4-1d). Effect-specific comprehensive SV_{LOW} values range from 0.000511 ug/L (Histopathology and Reproductive) to 2.27 ug/L (Mortality).

SV Point Estimates for Carbamazepine

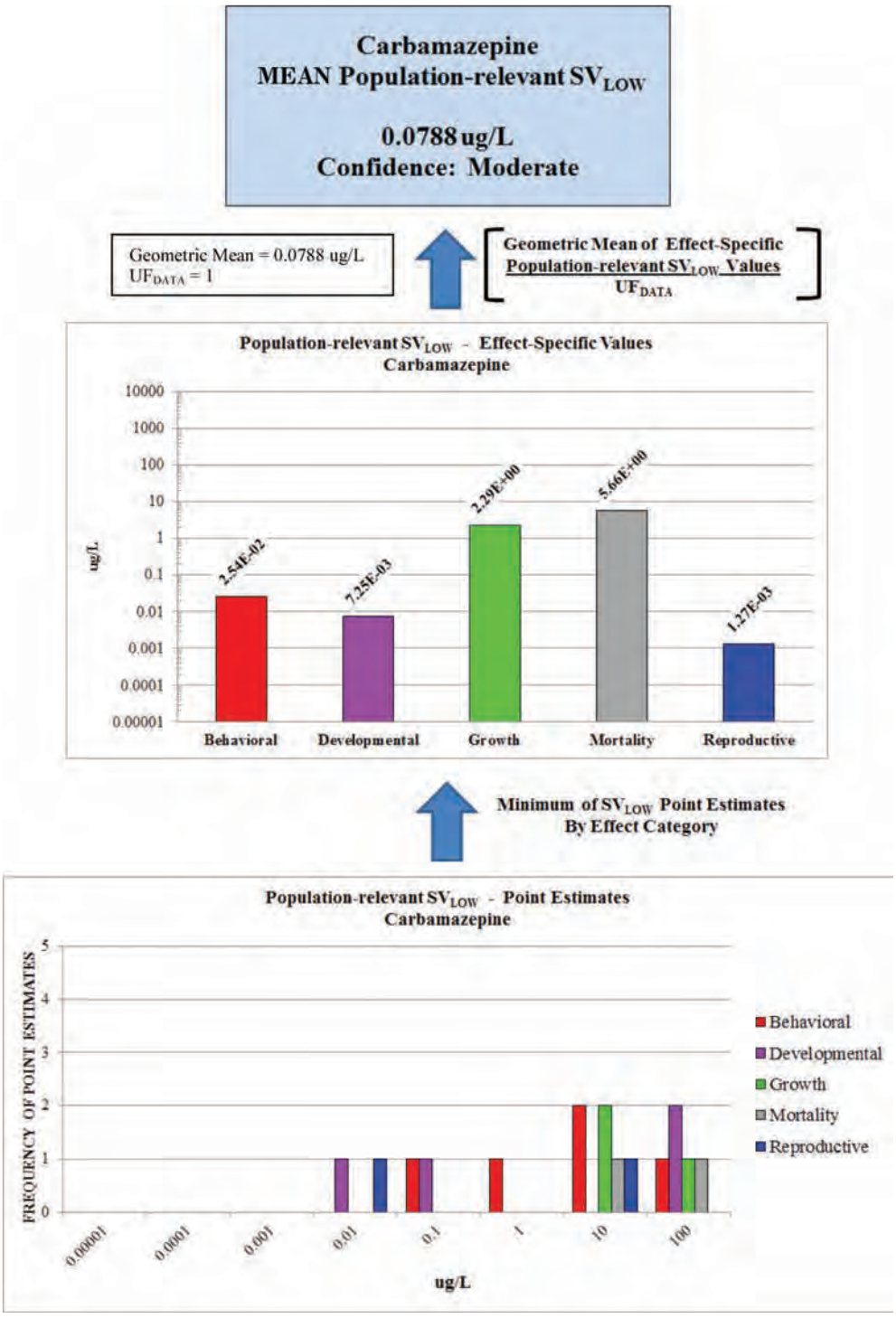
Effect Category	Carbamazepine Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	4.04 – 38,141 (6)	0.0254 – 525 (6)	3.79 – 35,760 (6)	0.0102 – 211 (7)
Developmental	3.25 – 49,292 (5)	0.0072 – 778 (6)	3.05 – 46,210 (5)	0.0029 – 313 (6)
Growth	719 (1)	2.29 – 42.2 (3)	674 (1)	0.92 – 16.9 (3)
Mortality	1,332 (1)	5.66 – 20.9 (2)	1,250 (1)	2.27 – 8.38 (2)
Reproductive	0.202 – 360 (2)	0.00127 – 2.26 (2)	0.19 – 337 (2)	0.00051 – 0.91 (2)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents			75.8 – 2,513 (2)	0.0026 – 6.78 (2)
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology			0.19 (2)	0.00051 (2)
Immunological				
Neurological			75.8 – 2,513 (2)	0.0026 – 6.78 (2)
Physiology/ Metabolism			68.2 – 2,513 (4)	0.0026 – 6.78 9 (4)

4.4.3.3. SV Development: Graphics for Carbamazepine

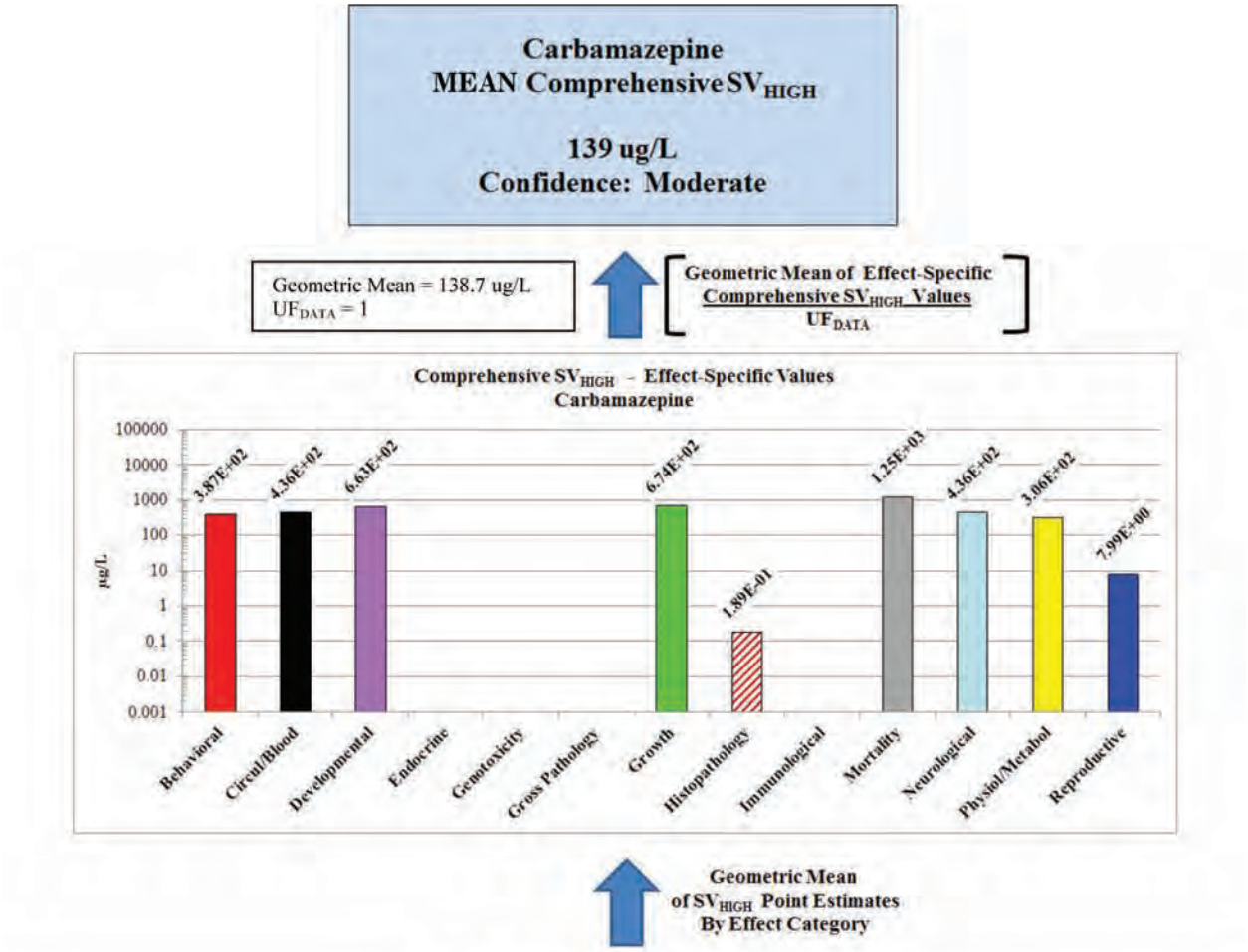
Population-relevant SV_{HIGH} Values for Carbamazepine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

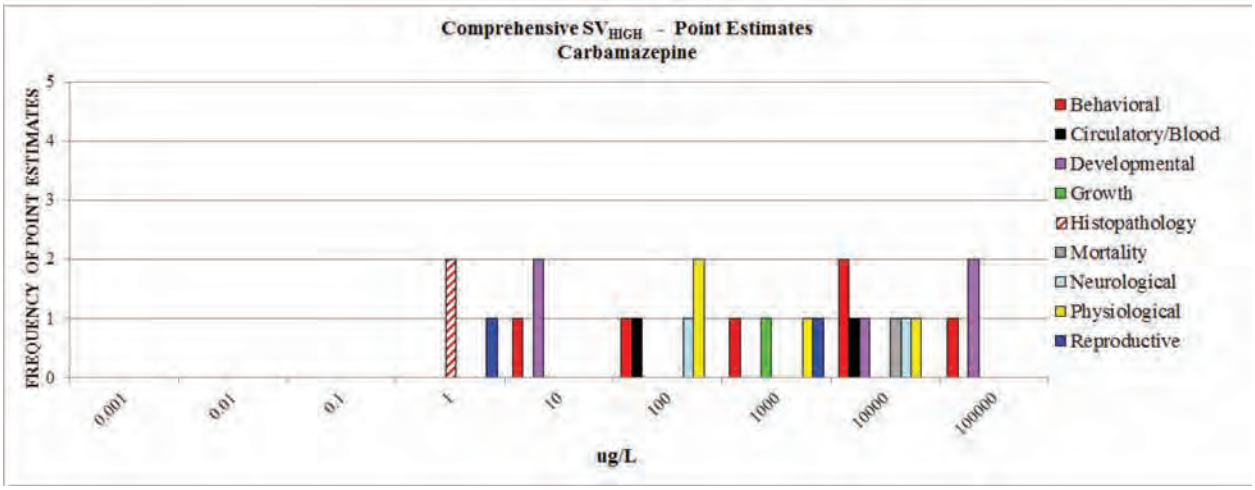


Population-relevant SV_{LOW} Values for Carbamazepine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

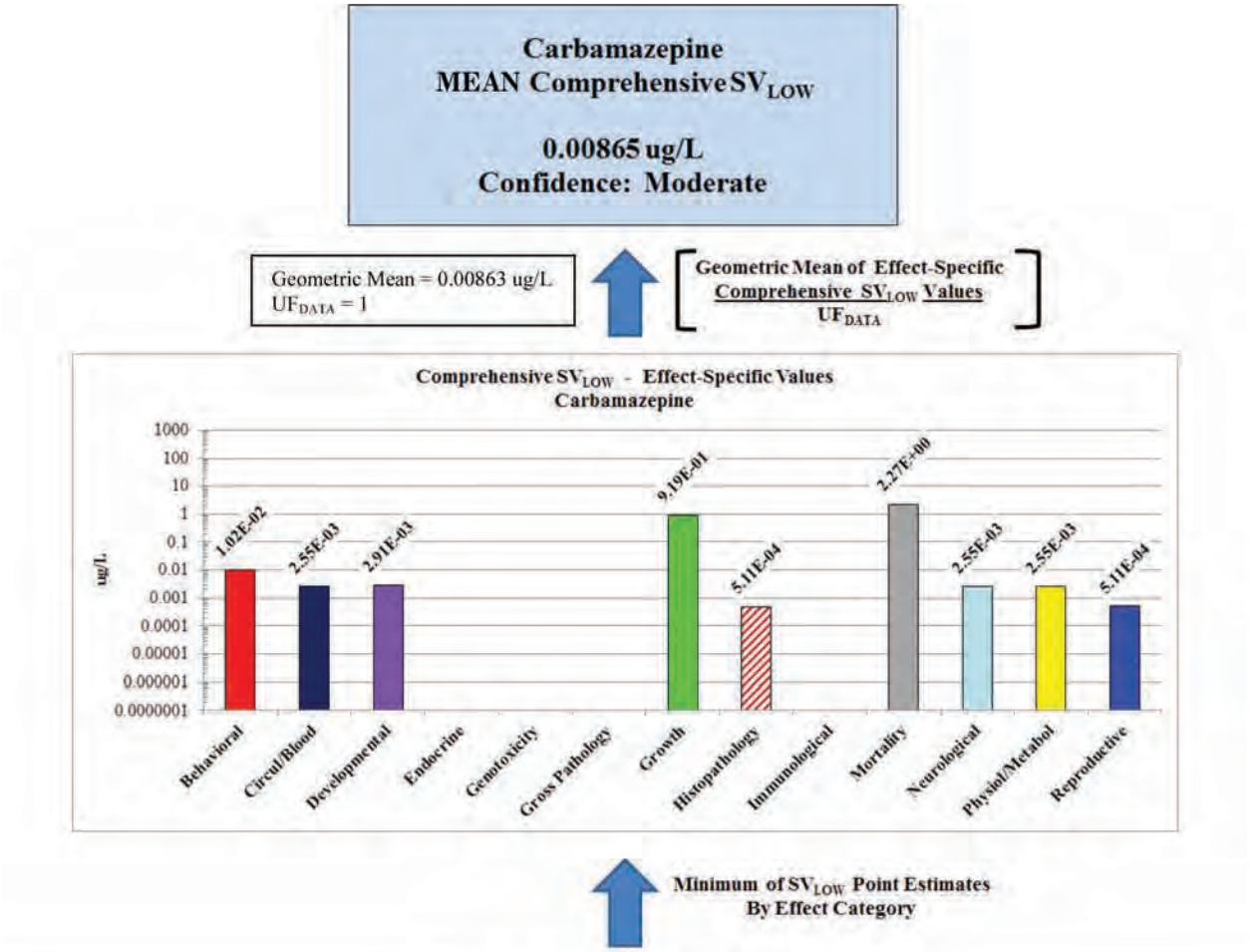


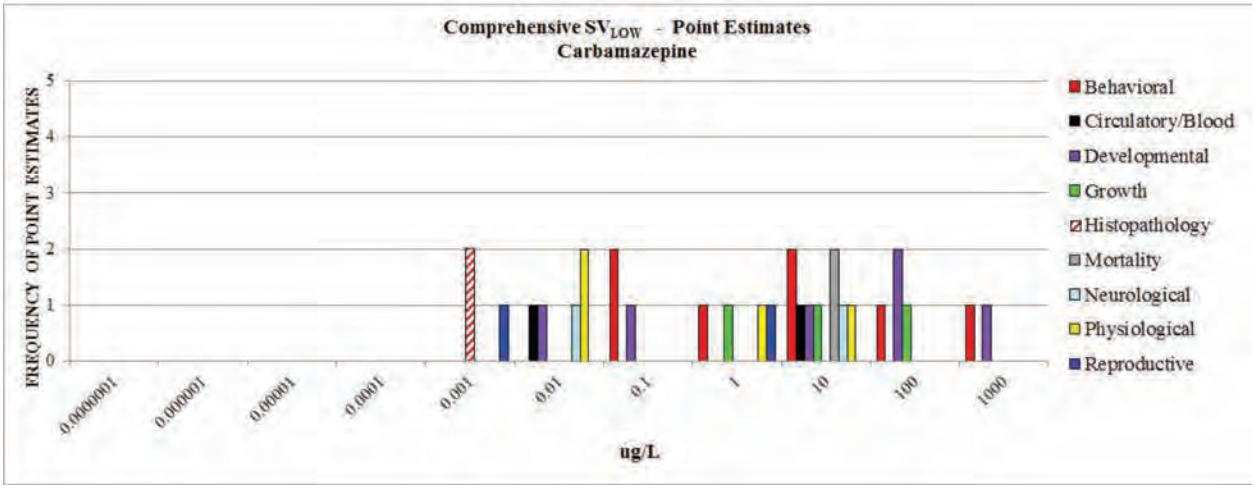
Comprehensive SV_{HIGH} Values for Carbamazepine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





Comprehensive SV_{LOW} Values for Carbamazepine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.4 Citalopram

4.4.4.1 Chemical Summary

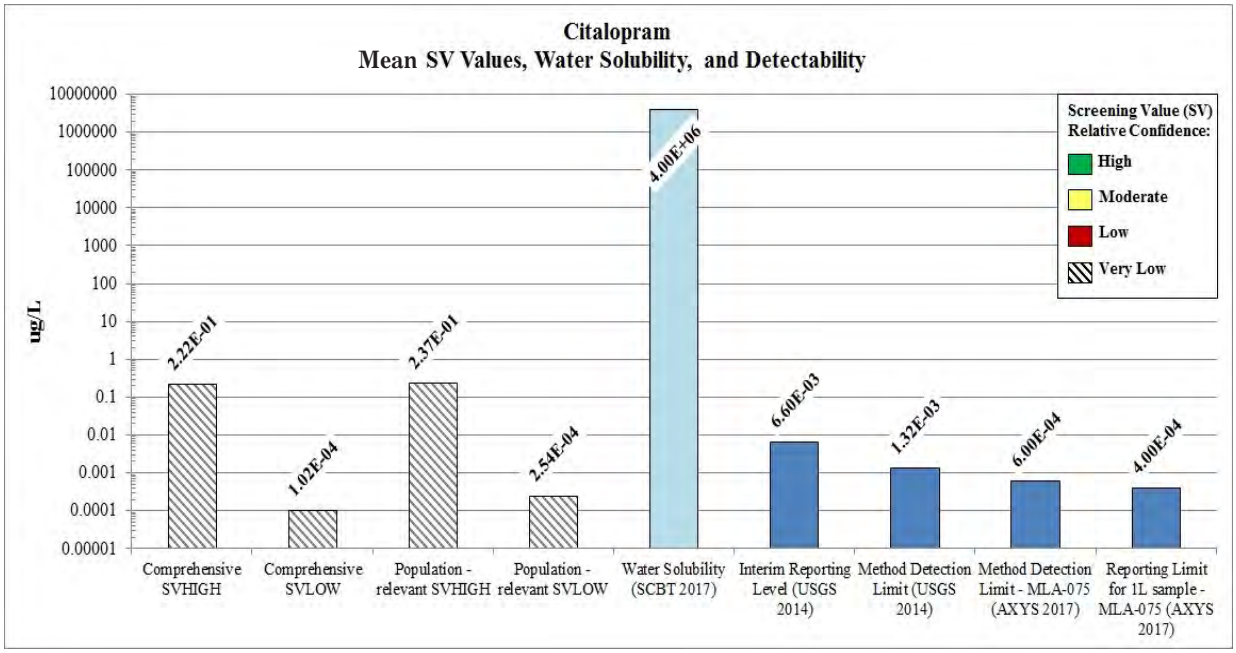
CEC Category: Pharmaceutical
CEC Subcategories: SSRI, antidepressant

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Citalopram is an antidepressant drug used to treat depression associated with mood disorders. It is also used on occasion in the treatment of body dysmorphic disorder and anxiety; Citalopram belongs to a class of drugs known as selective serotonin reuptake inhibitors (SSRIs)…."
- *CAS Number:* 59729-33-8
- *Water Solubility:* 4 mg/mL as citalopram hydrobromide (SCBT 2017)
- *logKow:* 3.5
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.08 ug/L*
- *Interim Reporting Level – Techniques and Methods 5-B10 (USGS 2014): 0.0066 ug/L*
- *MDL - Techniques and Methods 5-B10 (USGS 2014): 0.00132 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0006 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.0004 ug/L*

4.4.4.2 Screening Value Summary

Mean SV Values (ug/L) for Citalopram



Mean Population-relevant SV$_{HIGH}$ for Citalopram: 0.237 µg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category is represented.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Citalopram (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: guppy.
  - Life Stage(s): adult
  - Publication(s): Olsen et al. 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Behavioral (2): "freezing" behavior and time remaining frozen, five indicators of stress-related behavior
- *Cumulative Uncertainty Factor applied to the two LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Citalopram:* 4.95 *(see Attachment 4-2A for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Citalopram:* 5

Mean Population-relevant SV$_{LOW}$ for Citalopram: 0.000254 µg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category is represented
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Citalopram (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: guppy, rainbow trout
  - Life Stage(s): adult, fry
  - Publication(s): Holmberg et al. 2011, Olsen et al. 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Behavioral (5): "freezing" behavior and time remaining frozen, five indicators of stress-related behavior, courting behavior, sexual behavior, swimming activity, aggressive displays
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for Citalopram:* ranged from 157 to 472 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Citalopram:* 5

Mean Comprehensive SV$_{HIGH}$ for Citalopram: 0.22 µg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category is represented.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Citalopram (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: guppy.
  - Life Stage(s): adult
  - Publication(s): Olsen et al. 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - Behavioral (2): "freezing" behavior and time remaining frozen, five indicators of stress-related behavior
- *Cumulative Uncertainty Factor applied to the two LOAECs to obtain Comprehensive SV$_{HIGH}$ point estimates for Citalopram:* 5.28 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Citalopram:* 5

Mean Comprehensive SV$_{LOW}$ for Citalopram: 0.000102 µg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category is represented.
- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Citalopram (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: guppy, rainbow trout
  - Life Stage(s): adult, fry
  - Publication(s): Holmberg et al. 2011, Olsen et al. 2014
  - Effect Categories (Number of SV

Point Estimates), and Endpoints Evaluated in at least one Study

- Behavioral (5): "freezing" behavior and time remaining frozen, five indicators of stress-related behavior, courting behavior, sexual behavior, swimming activity, aggressive displays

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Citalopram:* ranged from 392 to 1175 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Citalopram:* 5

Effect Category-Specific SV Values (ug/L) for Citalopram

Population-relevant SV_{HIGH}: Data on citalopram are limited to the Behavioral effect category – 1.19 ug/L.

Population-relevant SV_{LOW} : Data are limited to the Behavioral effect category - 0.00127 ug/L.

Comprehensive SV_{HIGH} : Data on citalopram are limited to the Behavioral effect category – 1.11 ug/L.

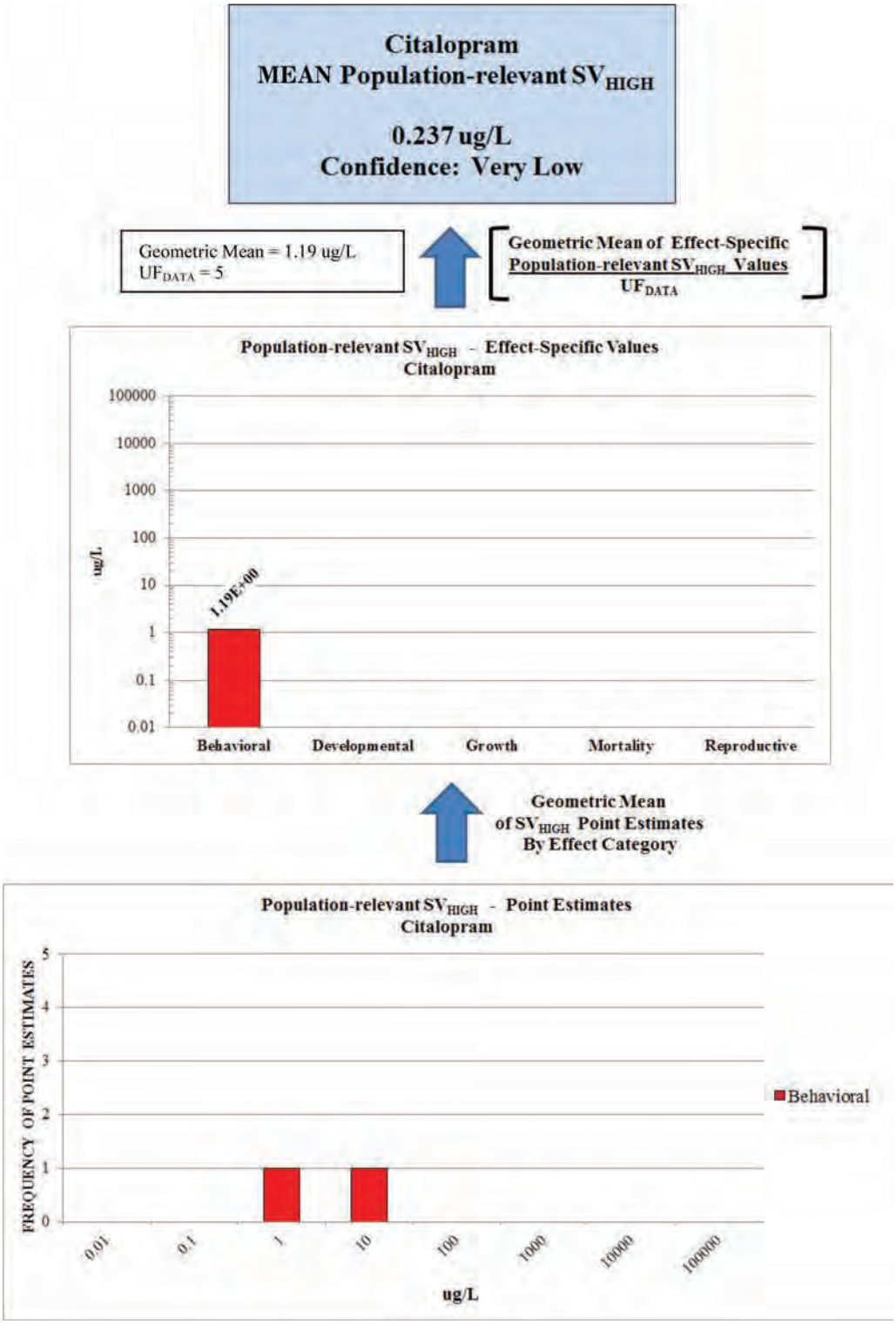
Comprehensive SV_{LOW} : Data are limited to the Behavioral effect category – 0.000511 ug/L.

SV Point Estimates for Citalopram

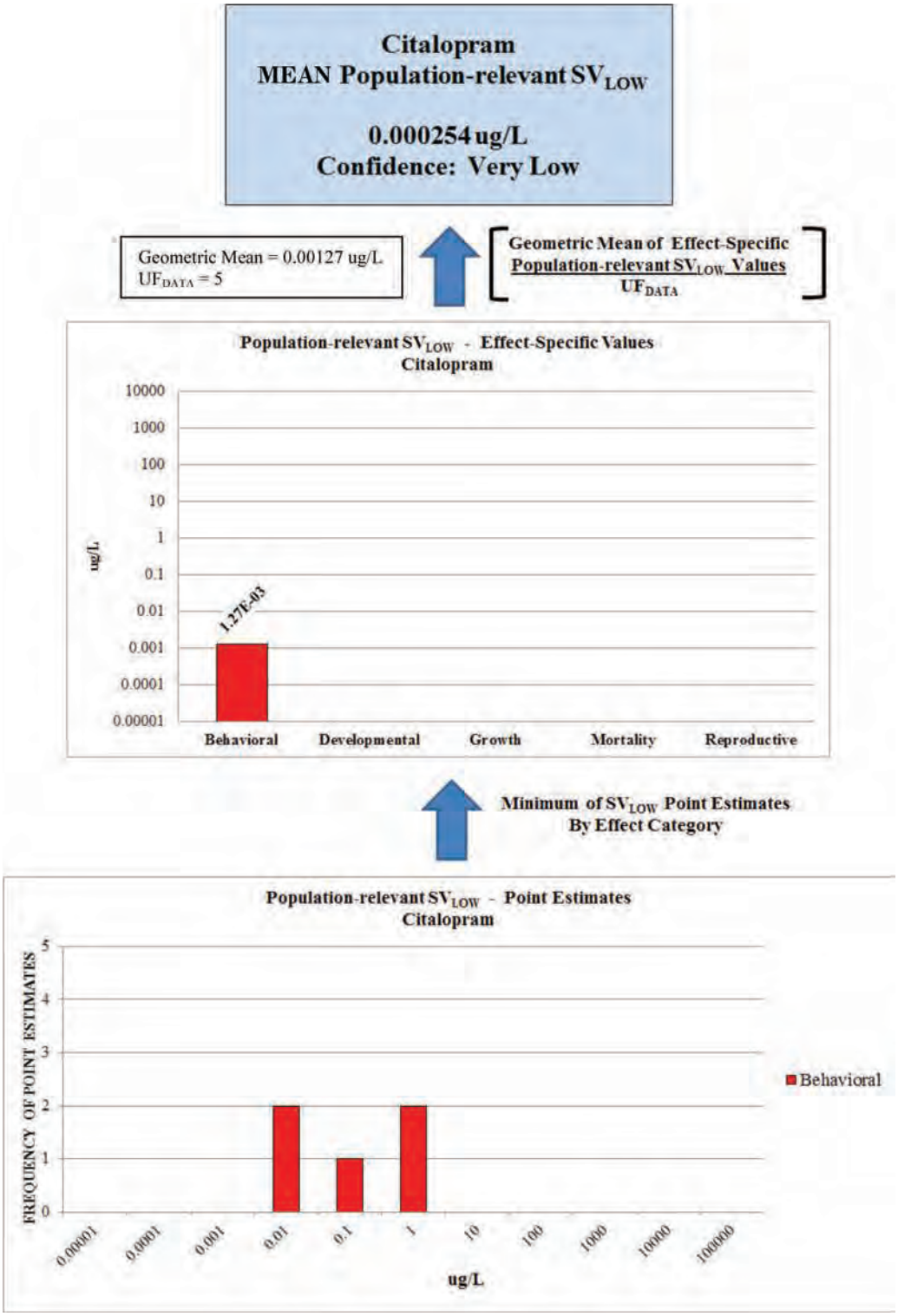
Effect Category	Citalopram Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive SVs				
Behavioral	0.46 – 3.03 (2)	0.00127 – 0.636 (5)	0.44 – 2.84 (2)	0.00051 – 0.255 (5)
Developmental				
Growth				
Mortality				
Reproductive				
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.4.3 SV Development: Graphics for Citalopram

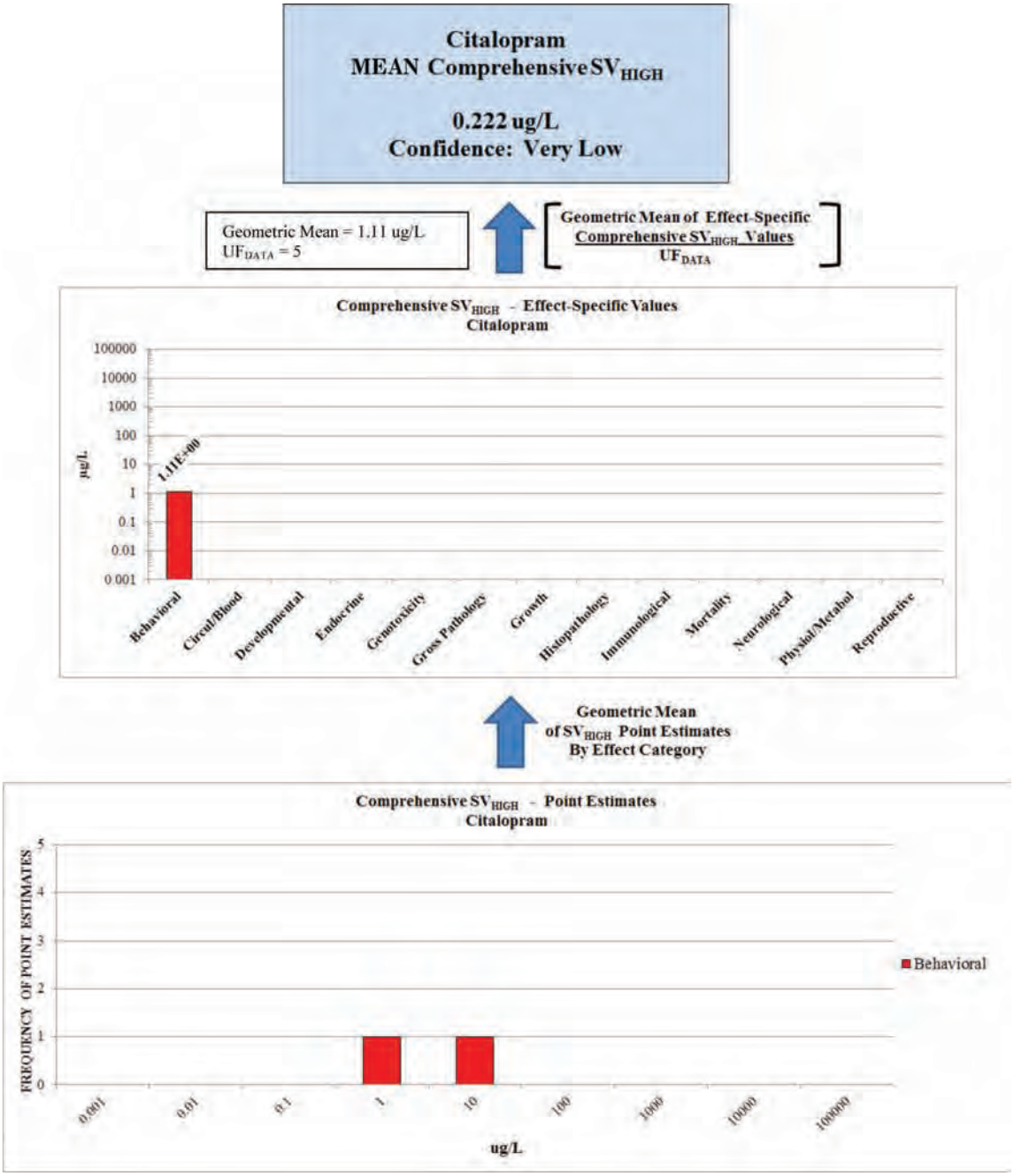
Population-relevant SV_{HIGH} Values for Citalopram: Relationships among the Mean Value, Effect-Specific Values, and Point Estimate s. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



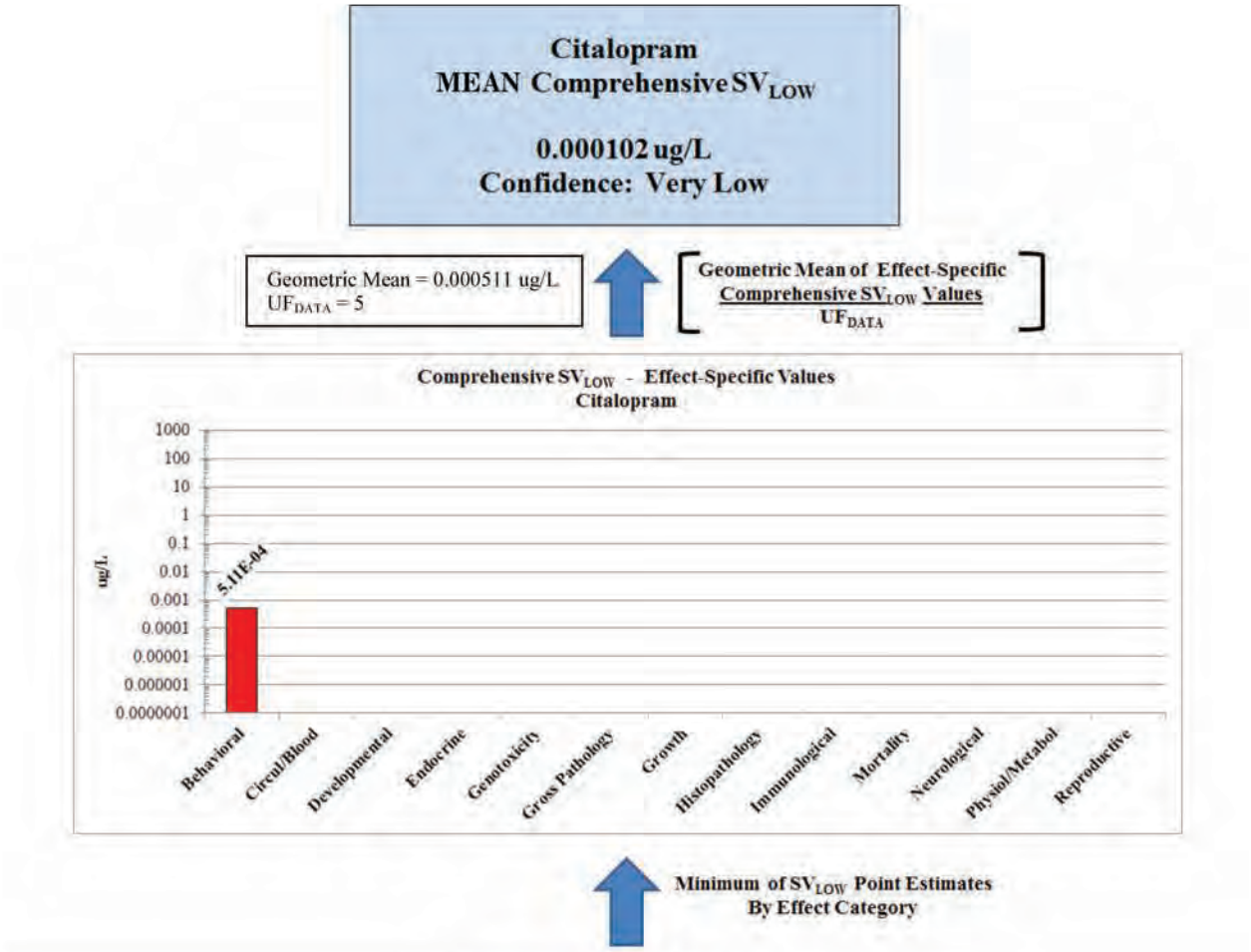
Population-relevant SV_{LOW} Values for Citalopram: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

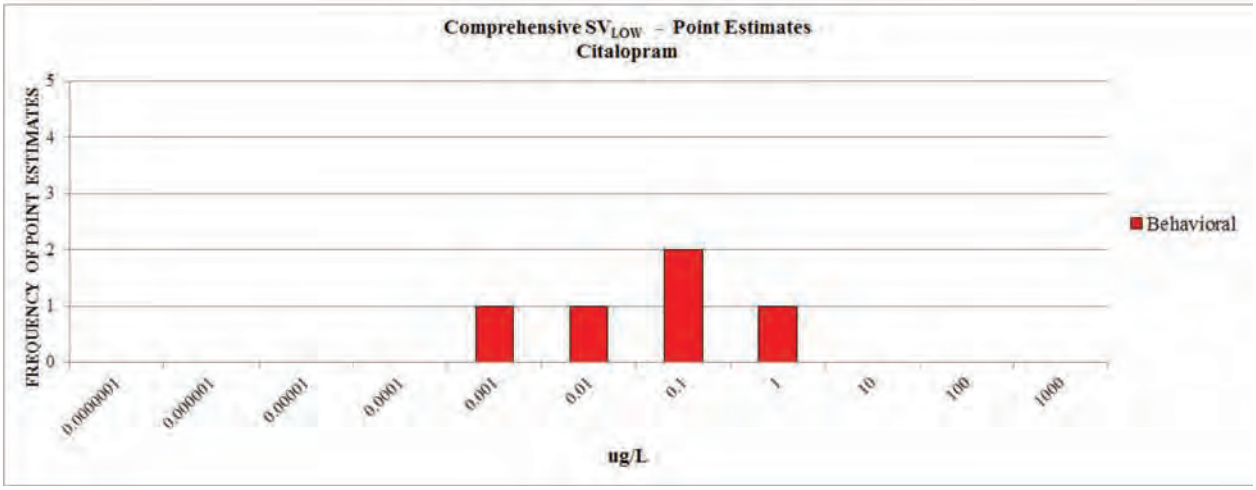


Comprehensive SV_{HIGH} Values for Citalopram: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Citalopram: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.5 N,N-diethyl-meta-toluamide (DEET)

4.4.5.1 Chemical Summary

CEC Category: Insect repellant

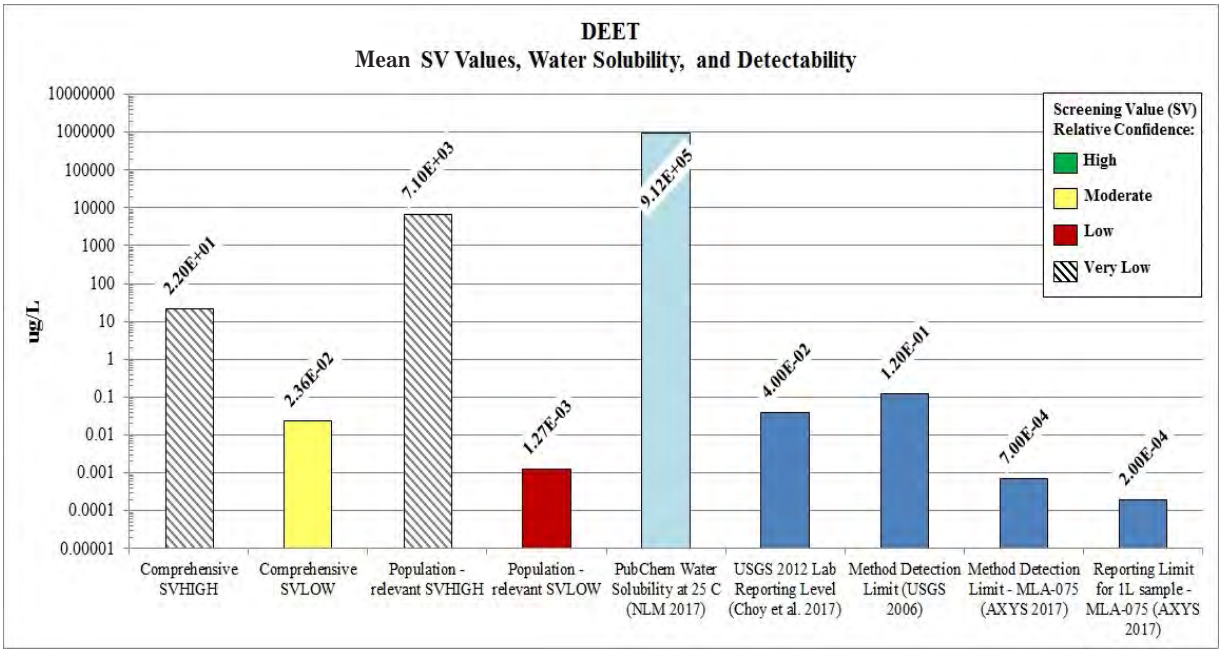
The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "DEET is a chemical (N,N-diethyl-meta-toluamide) used as the active ingredient in many insect repellent products…. It is now widely used, with approximately 30% of the U. S. population using DEET repellents each year… Approximately 230 products containing DEET are currently registered with the U. S. Environmental Protection Agency (EPA)."

- *CAS Number:* 134-62-3
- *Water Solubility:* 912 mg/L at 25 deg C (estimated)
- *logKow:* 2.02
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.04 ug/L*
- *MDL – Techniques and Methods 5-B4 (USGS 2006): 0.12 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0007 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.0002 ug/L*

4.4.5.2 Screening Value Summary

Mean SV Values (ug/L) for DEET



Mean Population-relevant SV$_{HIGH}$ for DEET: 7,098 μg/L

- *Relative Confidence:* Very Low. Only the Mortality effect category is represented, in only one fish species.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for DEET (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: mosquitofish
  - Life Stage(s): adult
  - Publication(s): Michael and Grant 1974
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Mortality (2)
- *Cumulative Uncertainty Factor applied to the two LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for DEET:* 7.425 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for DEET:* 3

Mean Population-relevant SV$_{LOW}$ for DEET: 0.00127 μg/L

- *Relative Confidence:* Low. Although three of the five population-relevant effect categories are represented, there are a total of only six observations based on few effect endpoints
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for DEET (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: common carp, fathead minnow, mosquitofish
  - Life Stage(s): adult
  - Publication(s): Michael and Grant 1974, Slaninova et al. 2014, Zenobio et al. 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - Growth (2): body weight, condition factor
    - Mortality (3)
    - Reproductive (1): gonad weights, GSI
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for DEET: ranged from 236 to 1179 (see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for DEET:* 2

Mean Comprehensive SV$_{HIGH}$ for DEET: 22.0 μg/L

- *Relative Confidence:* Very Low. Only three of the 13 effect categories are represented by a total of only four point estimates.
- *Representation in the Comprehensive/ SV$_{HIGH}$ Dataset for DEET (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: common carp, fathead minnow, mosquitofish
  - Life Stage(s): adult
  - Publication(s): Michael and Grant 1974, Slaninova et al. 2014, Zenobio et al. 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - Circulatory/Blood Constituents (1): 21 hematological and blood chemistry parameters
    - Endocrine/Hormone (1): androgen receptor gene expression in ovaries and 9 additional endocrine-related gene expressions
    - Mortality (2)
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for DEET:* ranged from 5.3 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for DEET:* 3

Mean Comprehensive SV$_{LOW}$ for DEET: 0.0236 μg/L

- *Relative Confidence:* Moderate. Eight of the 13 effect categories are represented using effects data from three fish species, but six of the effect categories have only one SV point estimate.

- *Representation in the Comprehensive SVLOW Dataset for DEET (see Attachment 4-2D: Comprehensive SVLOW Point Estimates)*
    - Species: common carp, fathead minnow, mosquitofish
    - Life Stage(s): adult
    - Publication(s): Michael and Grant 1974, Slaninova et al. 2014, Zenobio et al. 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
        - Circulatory/Blood Constituents (1): 21 hematological and blood chemistry parameters
        - Endocrine/Hormone (1): androgen receptor gene expression in ovaries and 9 additional endocrine-related gene expressions
        - Growth (2): body weight, condition factor
        - Histopathology (1): liver, gills, kidneys
        - Immunological (1): pro-inflammatory and anti-inflammatory gene expression
        - Mortality (3)
        - Physiology/Metabolism (1): activities of five antioxidant enzymes in liver and kidneys
        - Reproductive (1): gonad weights, GSI
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and unbounded LOAEC values to obtain Comprehensive SVLOW point estimates for DEET*: ranged from 587 to 2937 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SVLOW value from Effect-Specific SVLOW values for DEET*: 1

Effect-Specific SV Values (ug/L) for DEET

Population-relevant SV_{HIGH}: The DEET Population SV_{HIGH} for Mortality is 21,300 ug/L (Table 4-1a). Relevant data are limited to two SV_{HIGH} point estimates based on mortality in mosquitofish, ranging from 16,835 ug/L to 26,936 ug/L.

Population-relevant SV_{LOW}: Data were sufficient to estimate SVs for three of the five population-relevant effect categories (Table 4-1b). The Population SV_{LOW} value is the same, 0.00254 ug/L, for the Growth, Mortality, and Reproductive effect categories.

Comprehensive SV_{HIGH}: Data were sufficient to estimate SVs for three of the 13 effect categories (Table 4-1c). Effect-specific comprehensive SV_{LOW} values range from 0.076 ug/L (Endocrine) to 20,000 ug/L (Mortality).

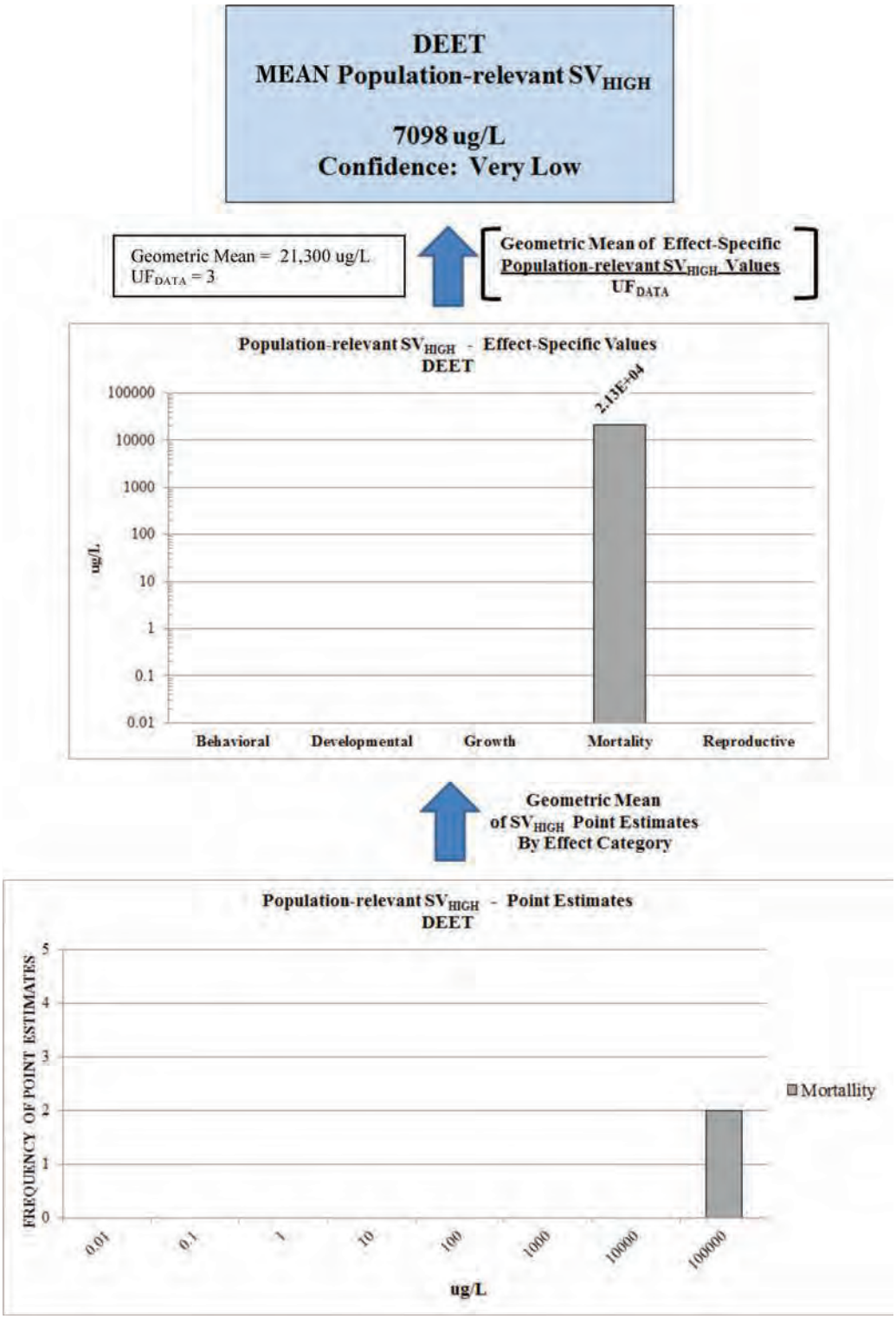
Comprehensive SV_{LOW}: Data were sufficient to estimate SVs for eight of the 13 effect categories (Table 4-1d). Effect-specific comprehensive SV_{LOW} values range from 0.00034 ug/L (Endocrine) to 1.28 ug/L (Histopathology, Immunological, Physiological/ Metabolic).

SV Point Estimates for DEET

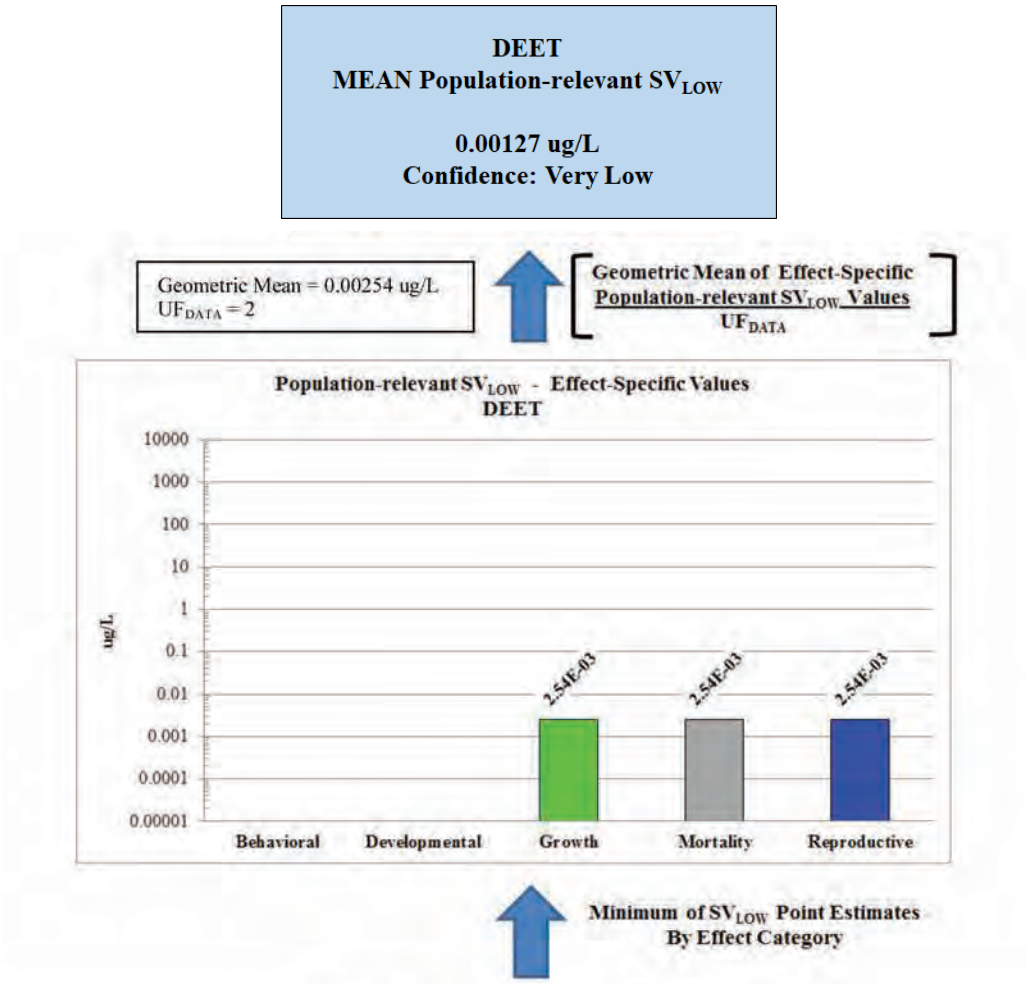
Effect Category	DEET Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral				
Developmental				
Growth		0.00254 – 3.18 (2)		0.00102 – 1.28 (2)
Mortality	16,835 – 26,936 (2)	0.00254 – 265 (3)	15,780 – 25,253 (2)	0.00102 – 106 (3)
Reproductive		0.00254 (1)		0.00102 (1)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents			189 (1)	0.13 (1)
Endocrine			0.076 (1)	0.00034 (1)
Genotoxicity				
Gross Pathology				
Histopathology				1.28 (1)
Immunological				1.28 (1)
Neurological				
Physiology/ Metabolism				1.28 (1)

4.4.5.3. SV Development: Graphics for DEET

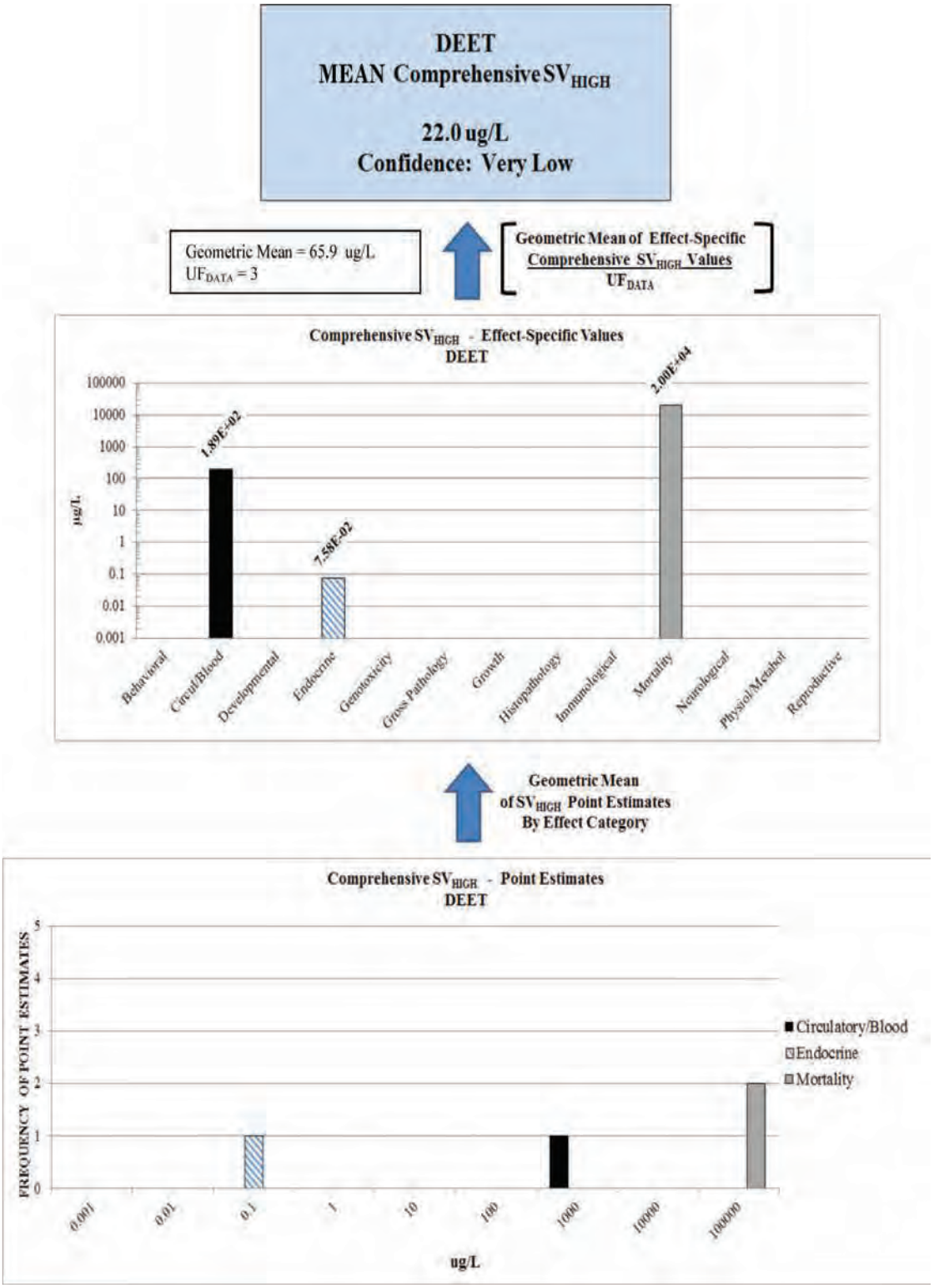
Population-relevant SV_{HIGH} Values for DEET: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



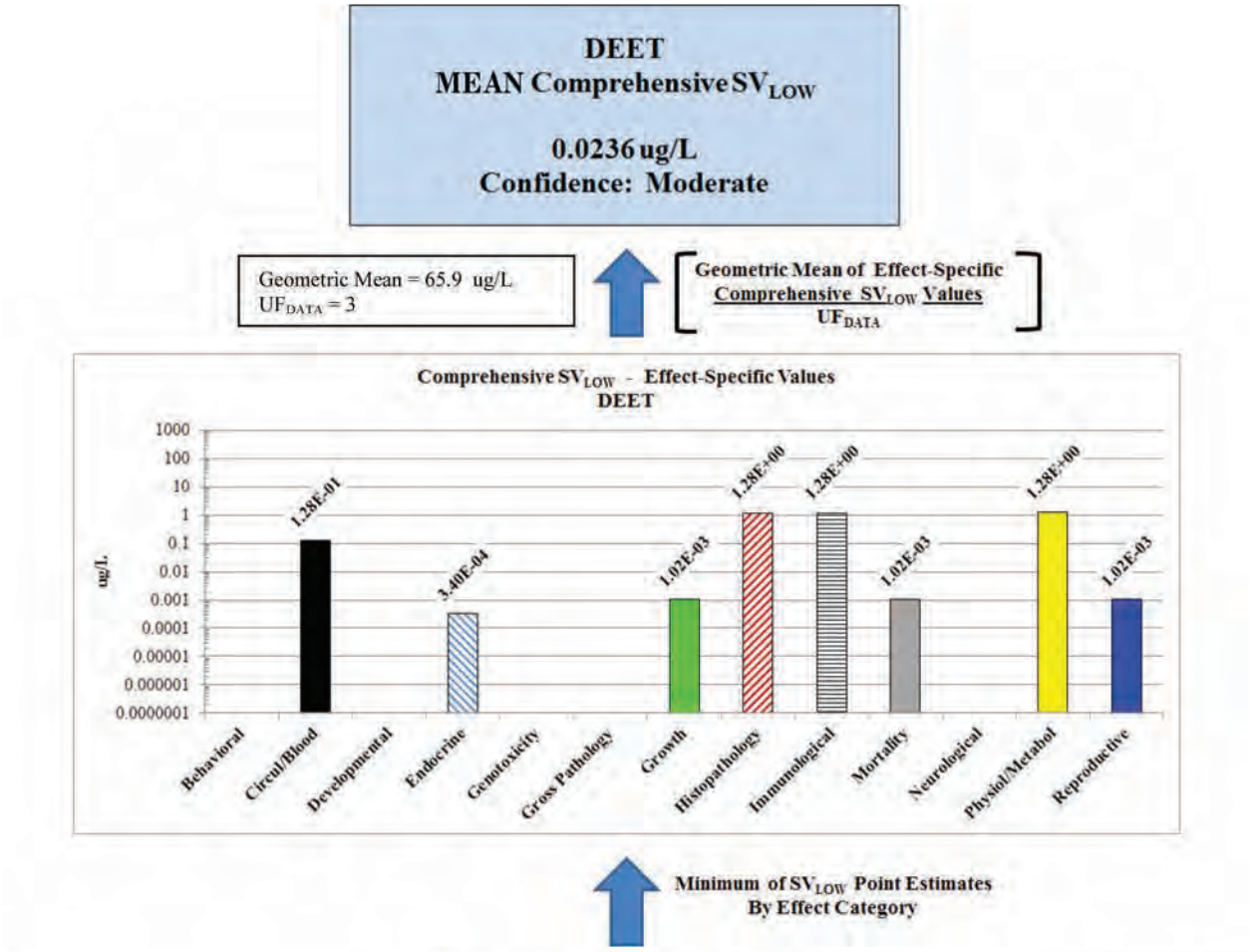
Population-relevant SV_{LOW} Values for DEET: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

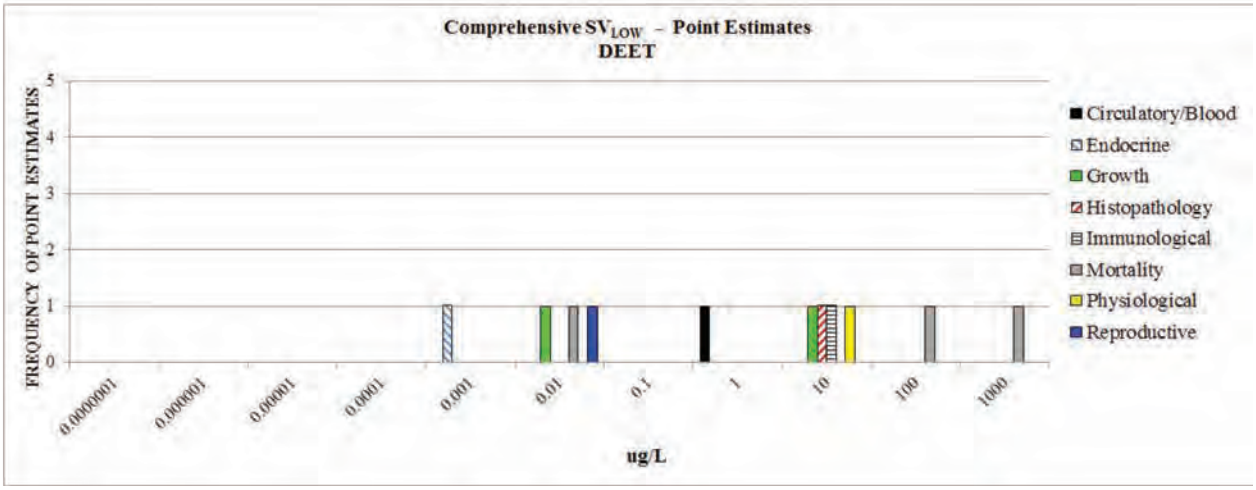


Comprehensive SV_{HIGH} Values for DEET: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals



Comprehensive SV_{LOW} Values for DEET: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.6 Diphenhydramine

4.4.6.1 Chemical Summary

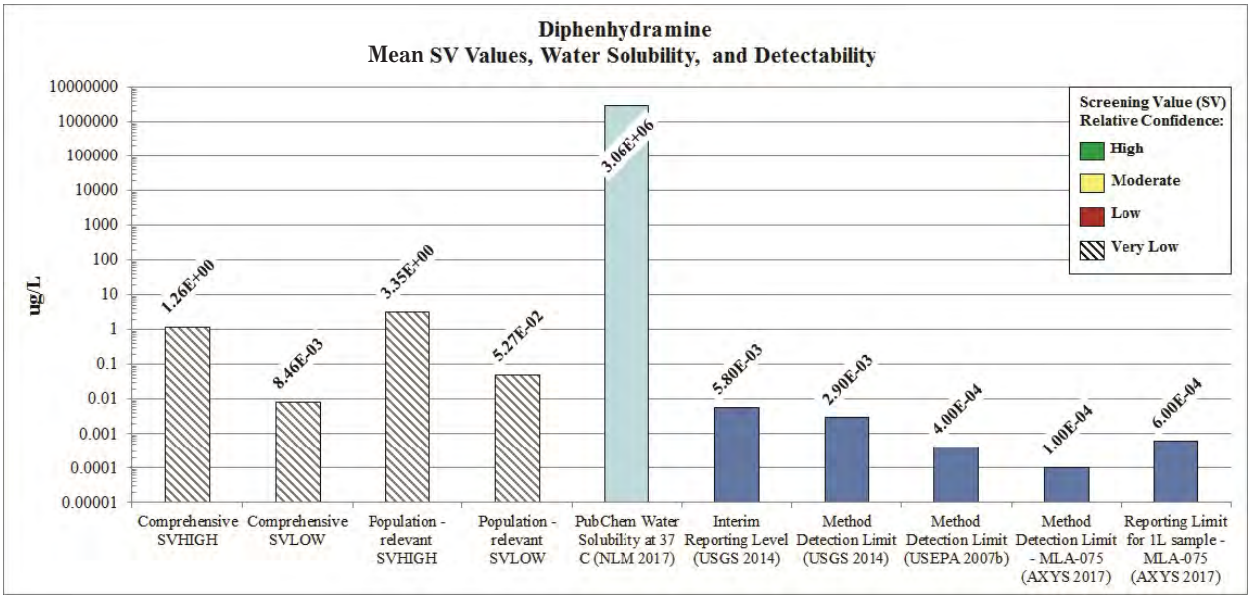
CEC Category: Pharmaceutical
CEC Subcategories: Antihistamine, antiallergenic

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Diphenhydramine is a first generation antihistamine and ethanolamine with sedative and anti-allergic properties. … This prevents histamine-induced bronchoconstriction, vasodilation, increased capillary permeability, and GI smooth muscle spasms."
- *CAS Number:* 58-73-1
- *Water Solubility:* 3060 mg/L (at 37 °C)
- *logKow:* 3.27
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.08 ug/L*
- *Interim Reporting Level – Techniques and Methods 5-B10 (USGS 2014): 0.0058 ug/L*
- *MDL - Techniques and Methods 5-B10 (USGS 2014): 0.0029 ug/L*
- *MDL – EPA Method 1694 (USEPA 2007b): 0.0004 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0001 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.0006 ug/L*

4.4.6.2 Screening Value Summary

Mean SV Values (ug/L) for Diphenhydramine



Mean Population-relevant SV$_{HIGH}$ for Diphenhydramine: 3.35 μg/L

- *Relative Confidence:* Very Low. The Behavioral and Developmental effect categories are represented by only one SV point estimate, each.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Diphenhydramine (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow
  - Life Stage(s): larva
  - Publication(s): Berninger et al. 2011
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* feeding rate
    - *Developmental (1):* growth, survival
- *Cumulative Uncertainty Factor applied to the two LOAECs to obtain Population-relevant SV$_{HIGH}$ point estimates for Diphenhydramine: 2.475 (see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Diphenhydramine:* 2

Mean Population-relevant SV$_{LOW}$ for Diphenhydramine: 0.0527 μg/L

- *Relative Confidence:* Very Low. The Behavioral and Developmental effect categories are represented by only one SV point estimate, each.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Diphenhydramine (see Attachment 4-2B: Population-elevant SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow
  - Life Stage(s): larva
  - Publication(s): Berninger et al. 2011
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* feeding rate
    - *Developmental (1):* growth, survival
- *Cumulative Uncertainty Factor applied to the two NOAECs to obtain Population relevant SV$_{LOW}$ point estimates for Diphenhydramine: 78.6 (see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Diphenhydramine:* 2

Mean Comprehensive SV$_{HIGH}$ for Diphenhydramine: 1.26 μg/L

- *Relative Confidence:* Very Low. The Behavioral and Developmental effect categories are represented by only one SV point estimate, each.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Diphenhydramine see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow
  - Life Stage(s): larva
  - Publication(s): Berninger et al. 2011
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* feeding rate
    - *Developmental (1):* growth, survival
- *Cumulative Uncertainty Factor applied to the two LOAECs to obtain Comprehensive SV$_{HIGH}$ point estimates for Diphenhydramine: 2.64 (see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Diphenhydramine:* 5

Mean Comprehensive SV$_{LOW}$ for Diphenhydramine: 0.00846 μg/L

- *Relative Confidence:* Very Low. The Behavioral and Developmental effect categories are represented by only one SV point estimate n, each.
- Representation in the Comprehensive SV$_{LOW}$ Dataset for Diphenhydramine see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)
  - Species: fathead minnow
  - Life Stage(s): larva
  - Publication(s): Berninger et al. 2011
  - Effect Categories (Number of SV Point Estimates), and Endpoints

Evaluated in at least one Study
- *Behavioral (1):* feeding rate
- *Developmental (1):* growth, survival

- *Cumulative Uncertainty Factor applied to the two NOAECs to obtain Comprehensive SVLOW point estimates for Diphenhydramine: 195.8 (see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SVLOW value from Effect-Specific SVLOW values for Diphenhydramine:* 5

Effect-Specific SV Values (ug/L) for Diphenhydramine

Population-relevant SVHIGH: The diphenhydramine effect-specific Population SVHIGH values for Behavioral and Developmental effects are 2.26 and 19.8 ug/L, respectively (Table 4-1a). Available data were not sufficient to develop effect-specific SV values for the other three population-relevant effect categories.

Population-relevant SVLOW : The effect-specific population SVLOW values for Behavioral and Developmental effects are 0.0356 and 0.312 ug/L, respectively (Table 4-1b). Available data were not sufficient to develop effect-specific SV values for the other three population-relevant effect categories.

Comprehensive SVHIGH : The effect-specific comprehensive SVHIGH values for Behavioral and Developmental effects are 2.12 and 18.6 ug/L, respectively (Table 4-1c). Available data were not sufficient to develop effect-specific SV values for the other 11 effect categories.

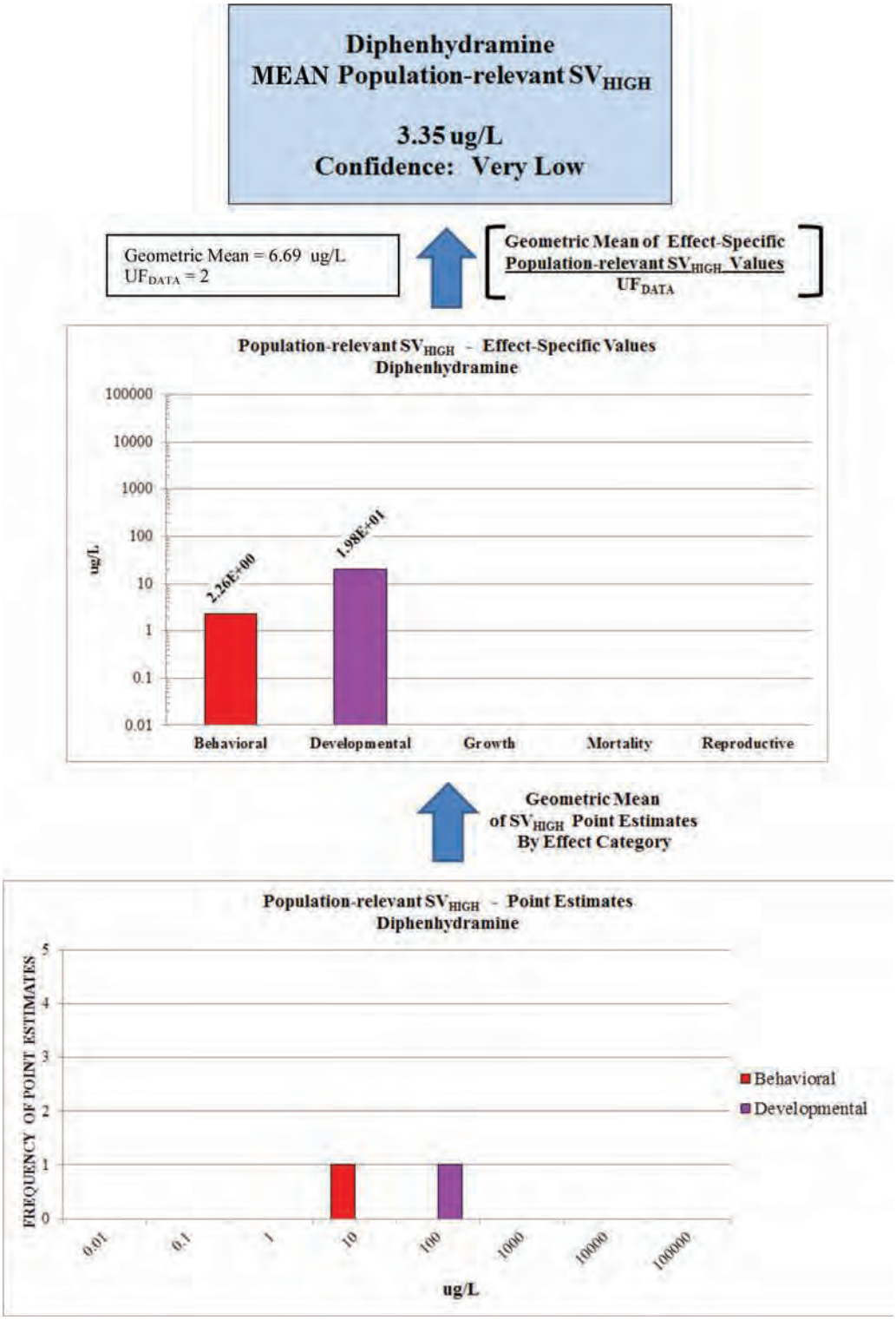
Comprehensive SVLOW : The effect-specific comprehensive SVLOW values for Behavioral and Developmental effects are 0.0143 and 0.125 ug/L, respectively (Table 4-1d). Available data were not sufficient to develop effect-specific SV values for the other 11 effect categories.

SV Point Estimates for Diphenhydramine

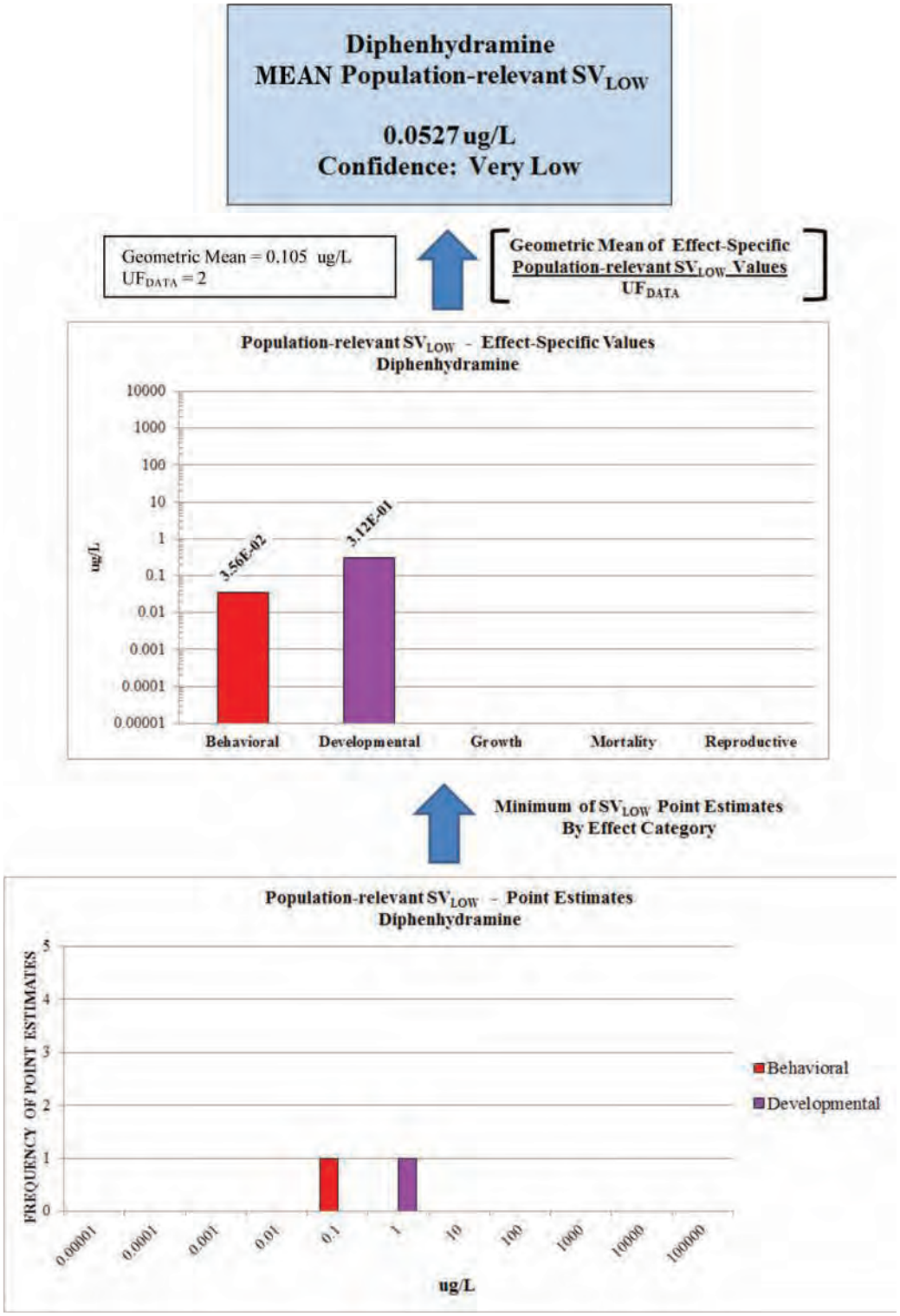
Effect Category	Diphenhydramine Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	2.26 (1)	0.036 (1)	2.12 (1)	0.014 (1)
Developmental	19.8 (1)	0.31 (1)	18.6 (1)	0.125 (1)
Growth				
Mortality				
Reproductive				
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.6.3 SV Development: Graphics for Diphenhydramine

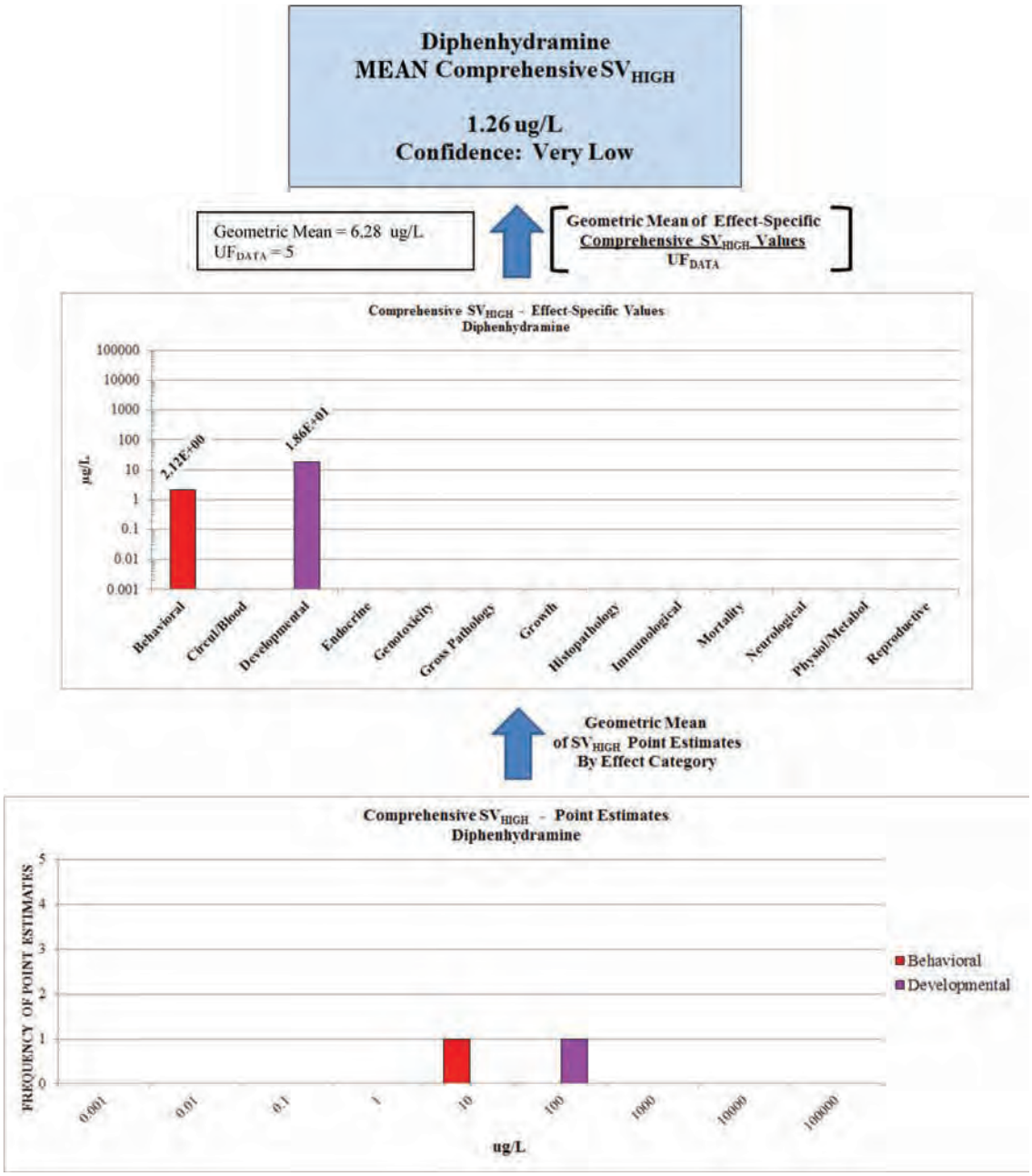
Population-relevant SV_{HIGH} Values for Diphenhydramine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals



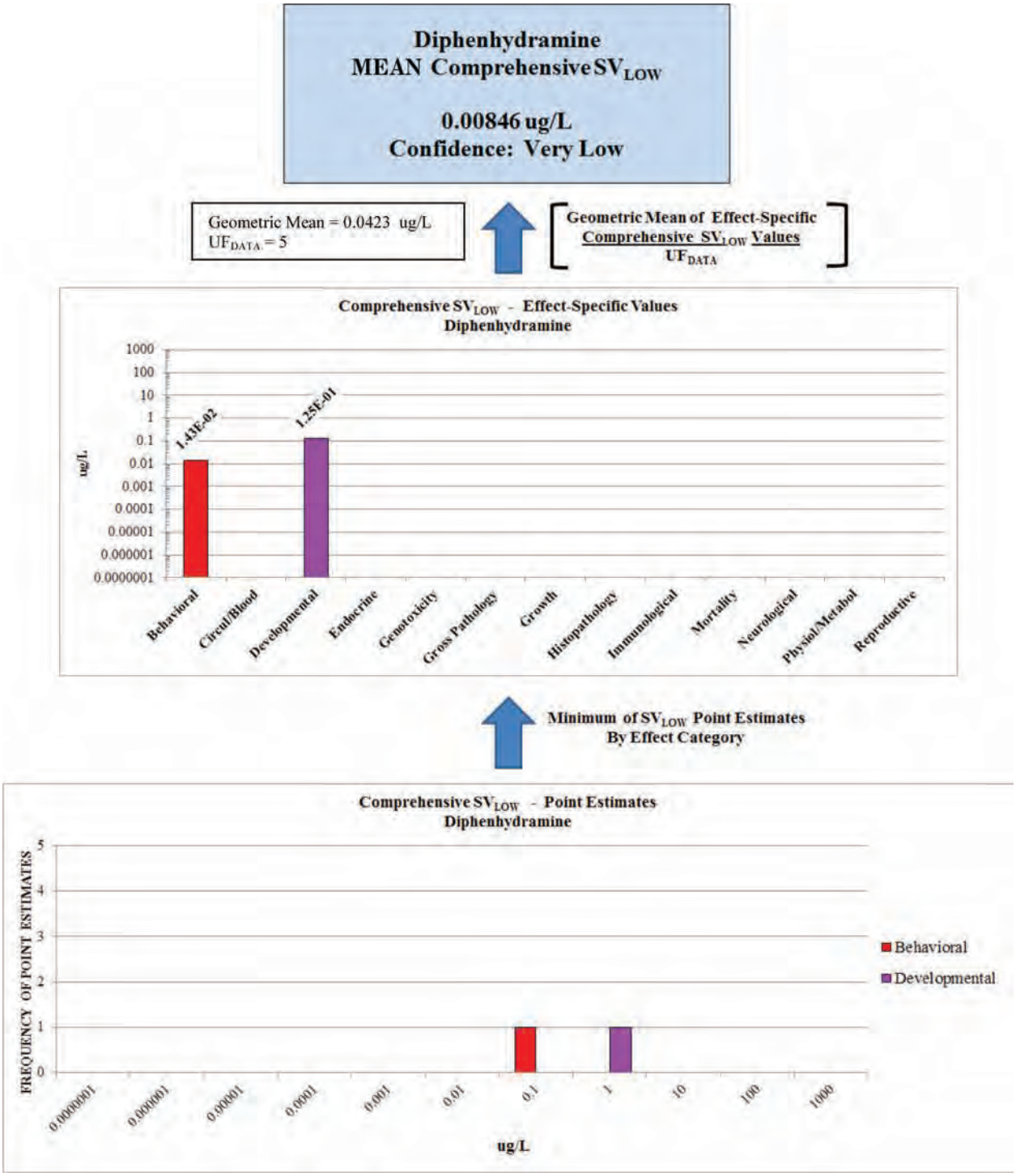
Population-relevant SV_{LOW} Values for Diphenhydramine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{HIGH} Values for Diphenhydramine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Diphenhydramine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



4.4.7 Estrone

4.4.7.1 Chemical Summary

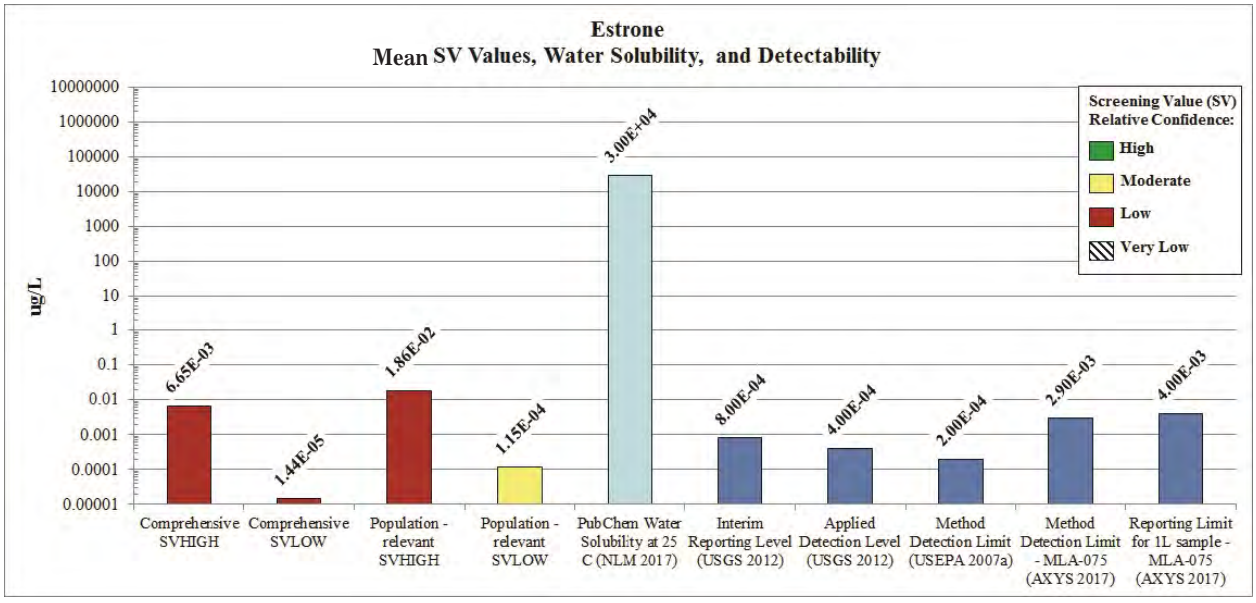
CEC Category: Hormone
CEC Subcategories: Therapeutic hormone, endogenous mammalian hormone

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Estrone is a major mammalian estrogen….Therapeutic Estrone is the synthetic form of a naturally occurring estrogen estrone. Estrone diffuses through the cell membrane and binds to and subsequently activates the nuclear estrogen receptor found in the reproductive tract, breast, pituitary, hypothalamus, liver, and bone."
- *CAS Number:* 53-16-7
- *Water Solubility:* 30 mg/L (at 25 °C)
- *logKow:* 3.13
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.0008 ug/L*
- *Interim Reporting Level - USGS Laboratory (USGS 2012): 0.0008 ug/L*
- *Applied Detection Level - USGS Techniques and Methods 5-B9 (USGS 2012): 0.0004 ug/L*
- *MDL - USEPA Method 1698 (USEPA 2007a): 0.0002 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0029 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.004 ug/L*

4.4.7.2 Screening Value Summary

Mean SV Values (ug/L) for Estrone



Mean Population-relevant SV$_{HIGH}$ for Estrone: 0.0186 µg/L

- *Relative Confidence:* Low. Although toxicity endpoints associated with three of the five population-relevant effect categories were reported in the literature, there are very few SV point estimates in two of the categories.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Estrone (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates*)
  - Species: fathead minnow, goldfish, Japanese medaka, Java medaka
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 6 separate studies published between 2001 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* escape response, response latency
    - *Developmental (4):* survival, hatchability, time to hatch, sex ratio, gross abnormalities, GSI, sex reversal in males, intersex, condition factor, growth, eosinophilia in kidneys and body cavity, egg production and fertility, HSI
    - *Reproductive (2):* reproductive hormone levels, GSI, gonadal DNA damage, spawning frequency, numbers eggs spawned, total eggs produced
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Estrone:* ranged from 2.5 to 5 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Estrone:* 2

Mean Population-relevant SV$_{LOW}$ for Estrone: 0.000115 µg/L

- *Relative Confidence:* Moderate. Effect endpoints associated with four of the five population-relevant effect categories were reported in the literature, however, there are few SV point estimates in two of the categories.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Estrone (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: brown trout, fathead minnow, goldfish, Japanese medaka, Java medaka, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 9 separate studies published between 1998 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (2):* escape response and response latency, larval behavioral tests
    - *Developmental (6):* survival, hatchability, time to hatch, sex ratio, gross abnormalities, GSI, sex reversal in males, intersex, total wet weight, condition factor, growth, eosinophilia in kidneys and body cavity, egg production and fertility, HSI
    - *Mortality (1)*
    - *Reproductive (4):* reproductive hormone levels, GSI, gonadal DNA damage, spawning frequency, numbers eggs spawned, total eggs produced
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for Estrone:* ranged from 78.6 to 315 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Estrone:* 1

Mean Comprehensive SV$_{HIGH}$ for Estrone: 0.00665 µg/L

- *Relative Confidence:* Low. Relevant data for only four of the 13 effect categories were located in the literature, and there are very few SV point estimates in two of those categories.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Estrone (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, goldfish, Japanese medaka, Java medaka, round goby, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 9 separate studies published between 1998 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* escape response, response latency
    - *Developmental (4):* survival, hatchability, time to hatch, sex ratio, gross abnormalities, GSI, sex reversal in males, intersex, condition factor, growth, eosinophilia in kidneys and body cavity, egg production and fertility, HSI
    - *Physiology/Metabolism (2):* basal ventilation
    - *Reproductive (4):* reproductive hormone levels, GSI, gonadal DNA damage, spawning frequency, numbers eggs spawned, total eggs produced
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for Estrone:* ranged from 2.6 to 13.2 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Estrone:* 3

Mean Comprehensive SV$_{LOW}$ for Estrone: 0.0000144 µg/L

- *Relative Confidence:* Low. Relevant data for only five of the 13 effect categories were located in the literature, and there are very few SV point estimates in three of those categories.
- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Estrone (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: brown trout, fathead minnow, goldfish, Japanese medaka, Java medaka, round goby, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 10 separate studies published between 1998 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (2):* escape response and response latency, larval behavioral tests
    - *Developmental (6):* survival, hatchability, time to hatch, sex ratio, gross abnormalities, GSI, sex reversal in males, intersex, total wet weight, condition factor, growth, eosinophilia in kidneys and body cavity, egg production and fertility, HSI
    - *Mortality (1)*
    - *Physiology/Metabolism (2):* basal ventilation
    - *Reproductive (4):* reproductive hormone levels, GSI, gonadal DNA damage, spawning frequency, numbers eggs spawned, total eggs produced
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SVLOW point estimates for Estrone:* ranged from 196 to 1958 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Estrone:* 1

Effect-Specific SV Values (ug/L) for Estrone

• Population-relevant SV_{HIGH}: The estrone effect-specific Population SV_{HIGH} values range from 0.0202 ug/L (Behavioral) to 0.0754 ug/L (Developmental). The Population SV_{HIGH} for the Reproductive effect category was intermediate (Table 4-1a).

• Population-relevant SV_{LOW} : Available data were sufficient to estimate values four of the five population-relevant effect categories. The effect-specific Population SV_{LOW} values range from 0.0000318 ug/L (Behavioral and Developmental) to 0.00168 (Mortality) (Table 4-1b).

• Comprehensive SV_{HIGH} : There were sufficient data to estimate values for only four of the 13 effect categories. Effect-specific comprehensive SV_{HIGH} values range from 0.00205 ug/L (Physiology/ Metabolism) to 0.0706 (Developmental) (Table 4-1c).

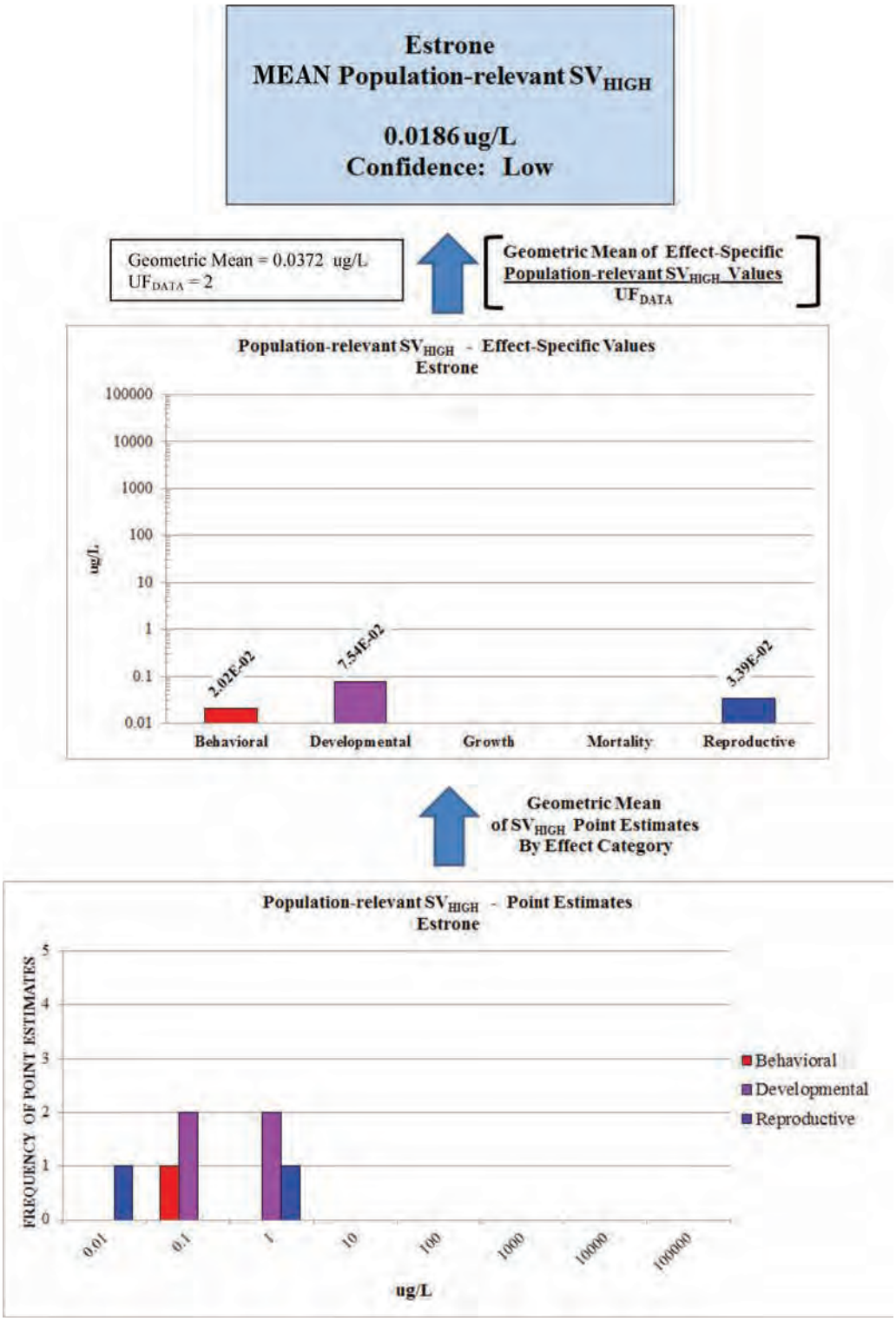
• Comprehensive SV_{LOW} : Five of the 13 effect categories have values for estrone (Table 4-1d). The effect-specific comprehensive SV_{LOW} values range from 0.000000138 ug/L (Physiology/ Metabolism) to 0.000674 ug/L (Mortality).

SV Point Estimates for Estrone

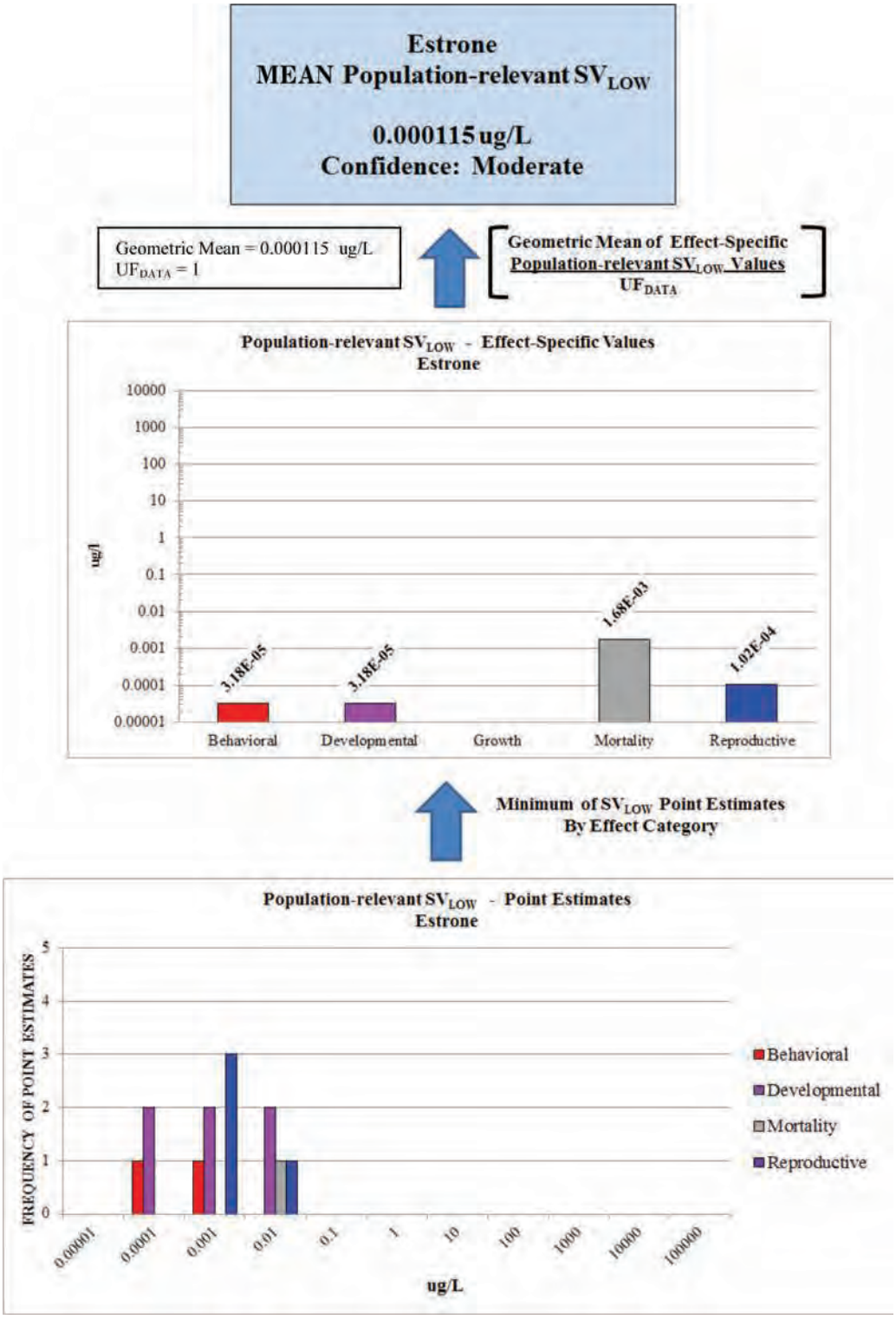
Effect Category	**Estrone Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category**			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	0.0202 (1)	0.0000318 – 0.000636 (2)	0.0189 (1)	0.0000128 – 0.000255 (2)
Developmental	0.0202 – 0.196 (4)	0.0000318 – 0.00252 (6)	0.0189 – 0.189 (4)	0.0000128 – 0.00101 (6)
Growth				
Mortality		0.00168 (1)		0.000674 (1)
Reproductive	0.0073 – 0.158 (2)	0.000102 – 0.00157 (4)	0.0068 – 0.187 (4)	0.0000409 – 0.000631 (4)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism			0.0002 – 0.0205 (2)	0.0000001 – 0.0000138 (2)

4.4.7.3 SV Development: Graphics for Estrone

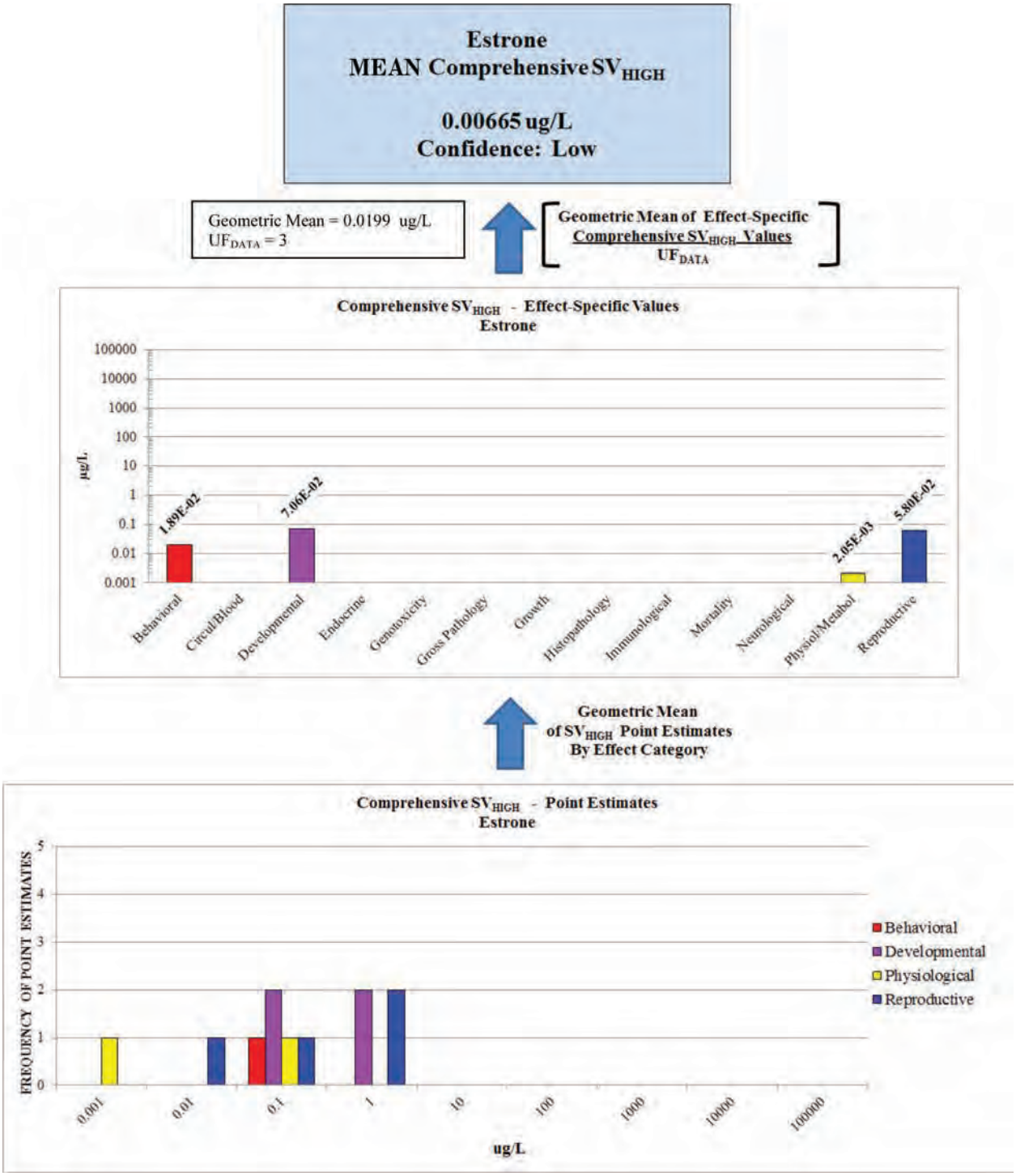
Population-relevant SV_{HIGH} Values for Estrone: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals



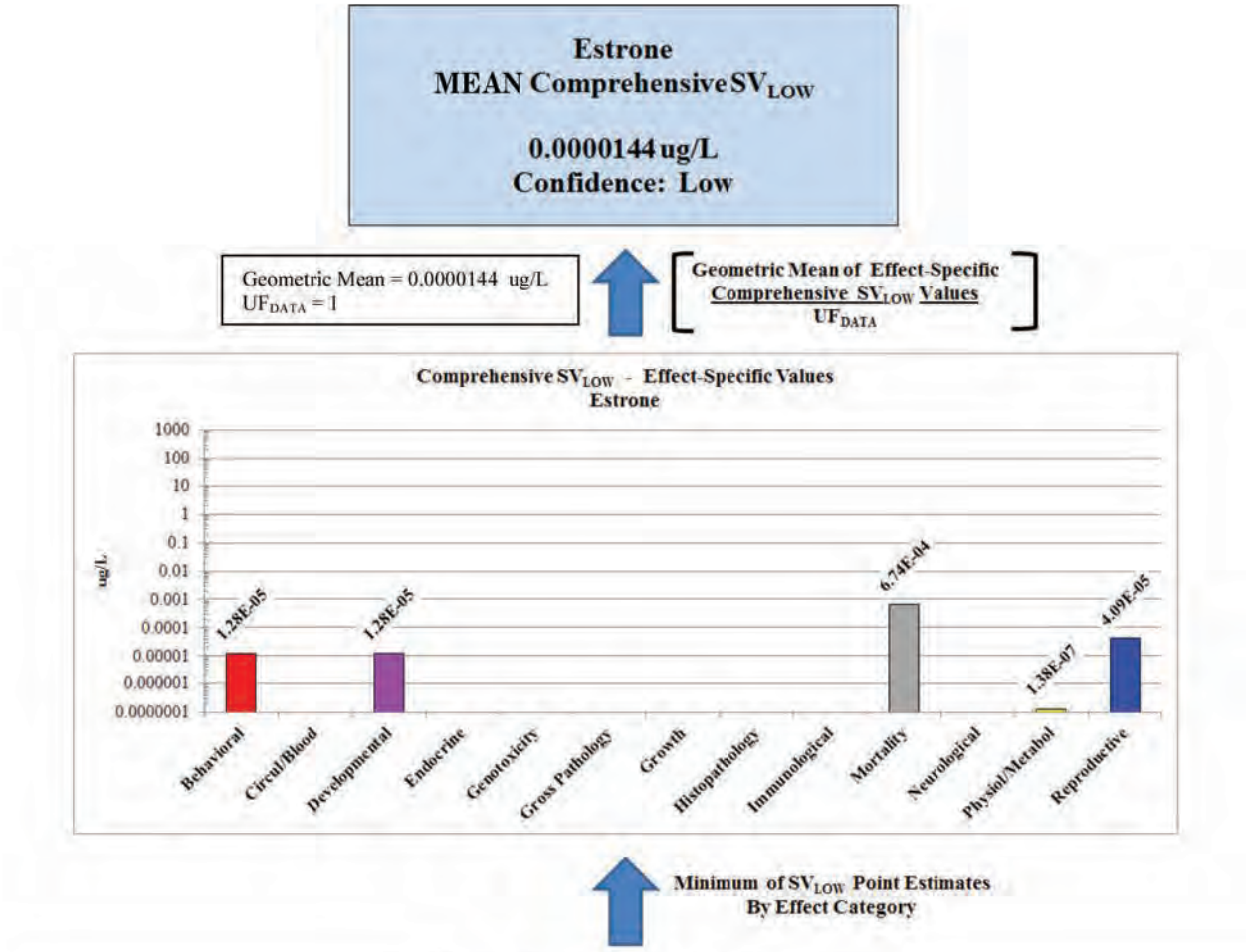
Population-relevant SV_{LOW} Values for Estrone: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

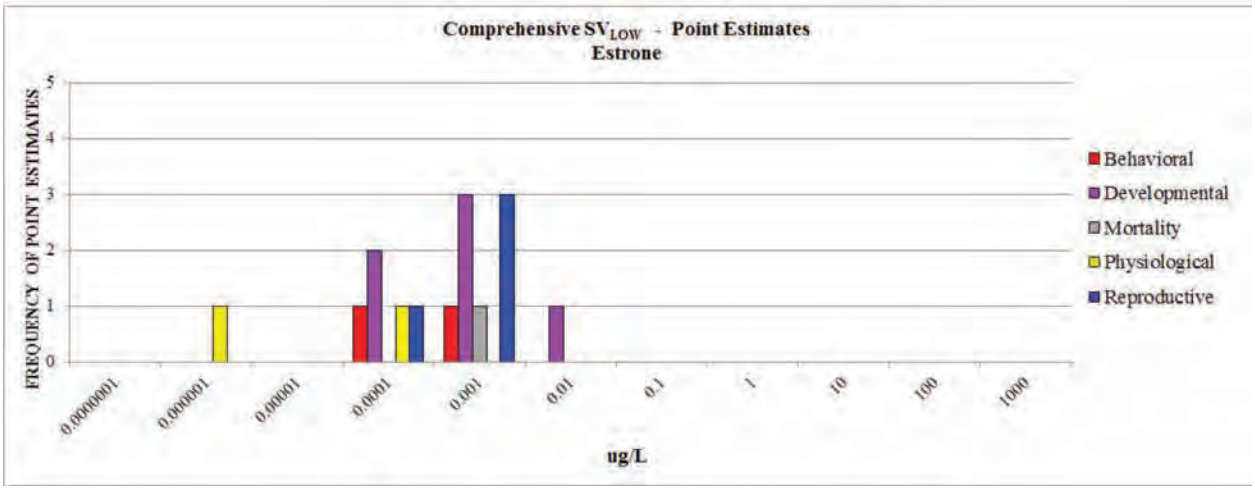


Comprehensive SV_{HIGH} Values for Estrone: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Estrone: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.8 Hexahydrohexamethylcyclopentabenzopyran (HHCB)

4.4.8.1 Chemical Summary

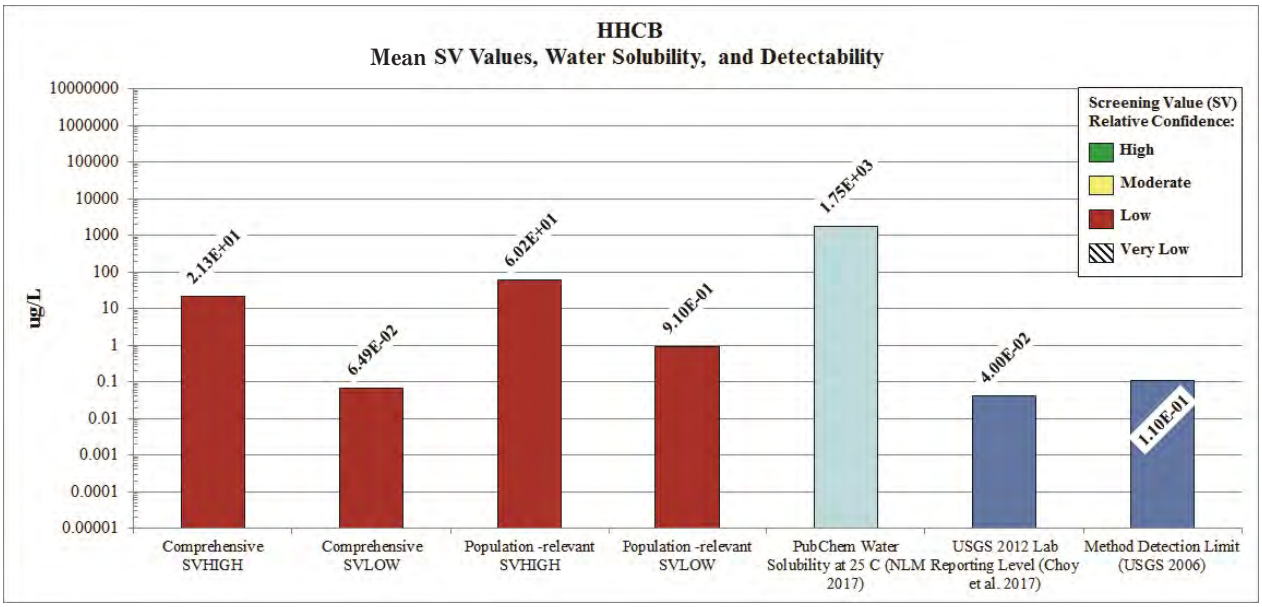
CEC Category: Fragrance
CEC Subcategory: Musk

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* HHCB is a musk fragrance used in air care products, cleaning products, soaps, plastic and rubber products, and personal care products. It has been identified as a High Production Volume chemical by the USEPA Office of Pollution Prevention and Toxics.
- *CAS Number:* 1222-05-5
- *Water Solubility:* 1.75 mg/L at 25 deg C
- *logKow:* 5.90
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 0.04 ug/L*
- *MDL – Techniques and Methods 5-B4 (USGS 2006): 0.11 ug/L*

4.4.8.2 Screening Value Summary

Mean SV Values (ug/L) for HHCB



Mean Population-relevant SV$_{HIGH}$ for HHCB: 60.2 µg/L

- *Relative Confidence:* Low. Although toxicity endpoints associated with four of the five population-relevant effect categories were reported in the literature, there is only one observation in each effect category. In addition, the two references (Croudace et al. 1997, Wüthrich 1996) were located only in secondary sources.

- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for HHCB (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*

    - Species: bluegill, fathead minnow
    - Life Stage(s): embryo, larva, adult
    - Publication(s): Croudace et al. 1997, Wüthrich 1996
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
        - *Behavioral (1):* respiration, equilibrium, righting reflex, swimming behavior
        - *Developmental (1):* survival, growth, balance and swimming behavior, activity level, hatchability
        - *Growth (1):* growth parameters
        - *Mortality* (1)

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for HHCB:* ranged from 2.5 to 5 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for HHCB:* 1

Mean Population-relevant SV$_{LOW}$ for HHCB: 0.91 µg/L

- *Relative Confidence:* Low. Although there were sufficient data to estimate values for four of the five population-relevant effect categories, three of the categories had only one observation. In addition, two of the three references (Croudace et al. 1997, Wüthrich 1996) were located only in secondary sources.

- *Representation in the Population-relevant SV$_{LOW}$ Dataset for HHCB (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*

    - Species: bluegill, fathead minnow, zebrafish
    - Life Stage(s): embryo, larva, adult
    - Publication(s): Carlsson and Norrgren 2004, Croudace et al. 1997, Wüthrich 1996
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
        - *Behavioral (1):* respiration, equilibrium, righting reflex, swimming behavior
        - *Developmental (2)*: survival, growth, balance and swimming behavior, activity level, hatchability, egg coagulation, tail extension, heartbeat and heart rate, edema, circulation
        - *Growth (1):* growth parameters
        - *Mortality (1)*

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for HHCB:* ranged from 78.6 to 157 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for HHCB:* 1

Mean Comprehensive SV$_{HIGH}$ for HHCB: 21.3 µg/L

- *Relative Confidence:* Low. Six of the 13 effect categories have minimally sufficient data to estimate a value – one observation per effect category. In addition, two of the four references (Croudace et al. 1997, Wüthrich 1996) were located only in secondary sources.

- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for HHCB (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*

    - Species: bluegill, fathead minnow, goldfish, zebrafish
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): Chen et al. 2012,

Croudace et al. 1997, Schreurs et al. 2004, Wüthrich 1996
- Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
  - *Behavioral (1):* respiration, equilibrium, righting reflex, swimming behavior
  - *Developmental (1):* survival, growth, balance and swimming behavior, activity level, hatchability
  - *Growth (1):* growth parameters
  - *Mortality (1)*
  - *Physiology/Metabolism (1):* oxidative stress indicators, antioxidant enzyme activity
  - *Reproductive (1):* anti-estrogenicity

o *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for HHCB:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for HHCB:* 1

Mean Comprehensive SV$_{LOW}$ for HHCB: 0.0649 µg/L

o *Relative Confidence:* Low. Although relevant data are available for six of the 13 effect categories, five of the categories had only one observation each. In addition, two of the five references (Croudace et al. 1997, Wüthrich 1996) were located only in secondary sources.

o *Representation in the Comprehensive SV$_{LOW}$ Dataset for HHCB (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: bluegill, fathead minnow, goldfish, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Carlsson and Norrgren 2004, Chen et al. 2012, Croudace et al. 1997, Schreurs et al. 2004, Wüthrich 1996
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* respiration, equilibrium, righting reflex, swimming behavior
    - *Developmental (2):* survival, growth, balance and swimming behavior, activity level, hatchability, egg coagulation, tail extension, heartbeat and heart rate, edema, circulation
    - *Growth (1):* growth parameters
    - *Mortality (1)*
    - *Physiology/Metabolism (1):* oxidative stress indicators, antioxidant enzyme activity
    - *Reproductive (1):* anti-estrogenicity

o *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for HHCB:* ranged from 196 to 1175 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for HHCB:* 1

Effect-Specific SV Values (ug/L) for HHCB

• Population-relevant SV_{HIGH}: The HHCB effect-specific Population-relevant SV_{HIGH} values range from 36.8 ug/L (Behavioral) to 79.4 ug/L (Growth and Mortality) (Table 4-1a), although each effect category is represented by only one SV point estimate.

• Population-relevant SV_{LOW} : Available data were sufficient to estimate values four of the five population-relevant effect categories, although three of the categories have only one SV point estimate each. The effect-specific population-relevant SV_{LOW} values range from 0.591 ug/L (Behavioral) to 1.16 (Growth and Mortality) (Table 4-1b).

• Comprehensive SV_{HIGH} : There were minimally sufficient data to estimate values for only six of the 13 effect categories – one observation per category. Effect-specific comprehensive SV_{HIGH} values range from 2.84 ug/L (Physiology/Metabolism) to 74.4 ug/L (Growth and Mortality) (Table 4-1c).

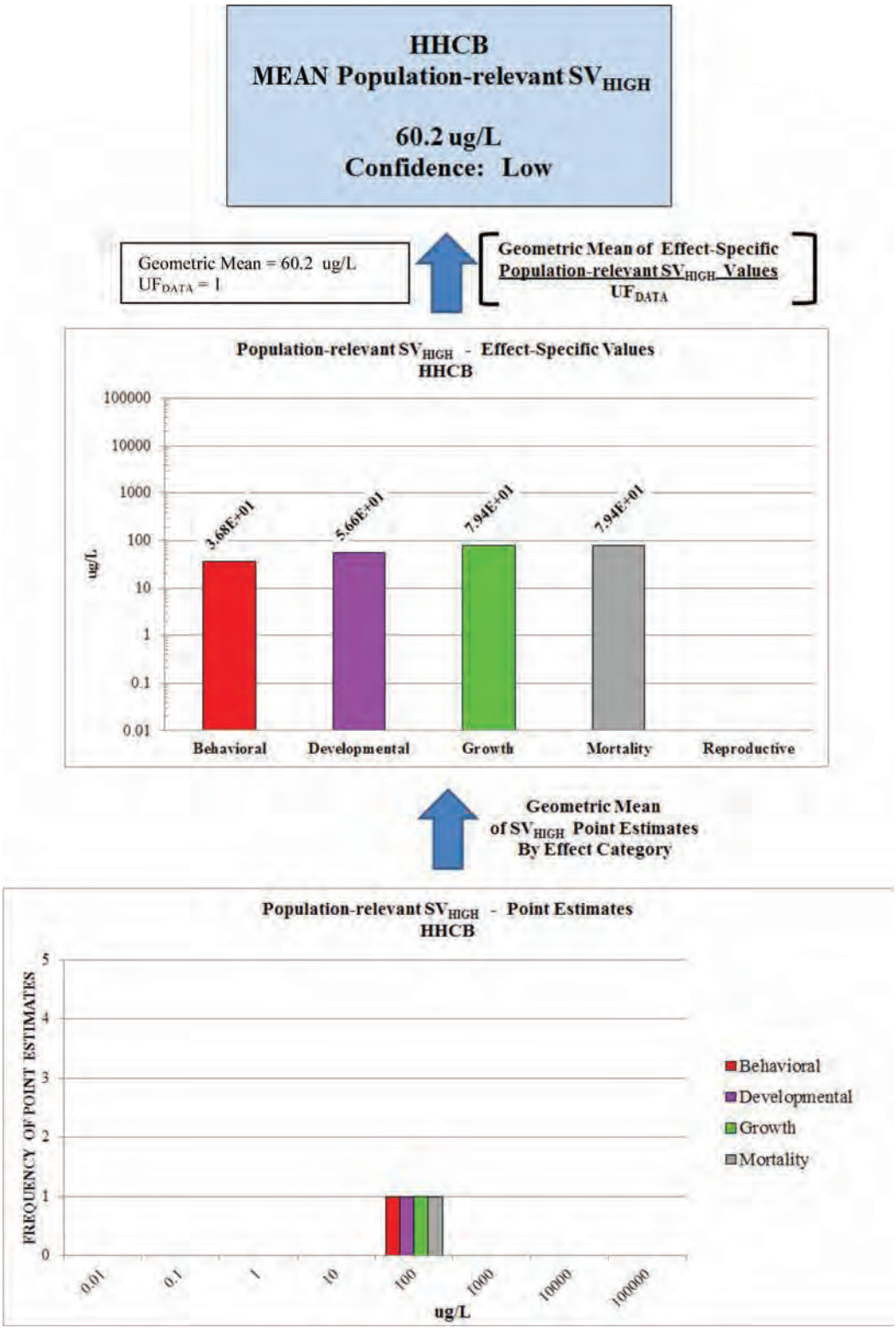
• Comprehensive SV_{LOW} : There were minimally sufficient data to estimate values for only six of the 13 effect categories, with only one SV point estimate in five of the categories. The effect-specific comprehensive SV_{LOW} values range from 0.00192 ug/L (Physiology/Metabolism) to 0.465 ug/L (Growth and Mortality) (Table 4-1d).

SV Point Estimates for HHCB

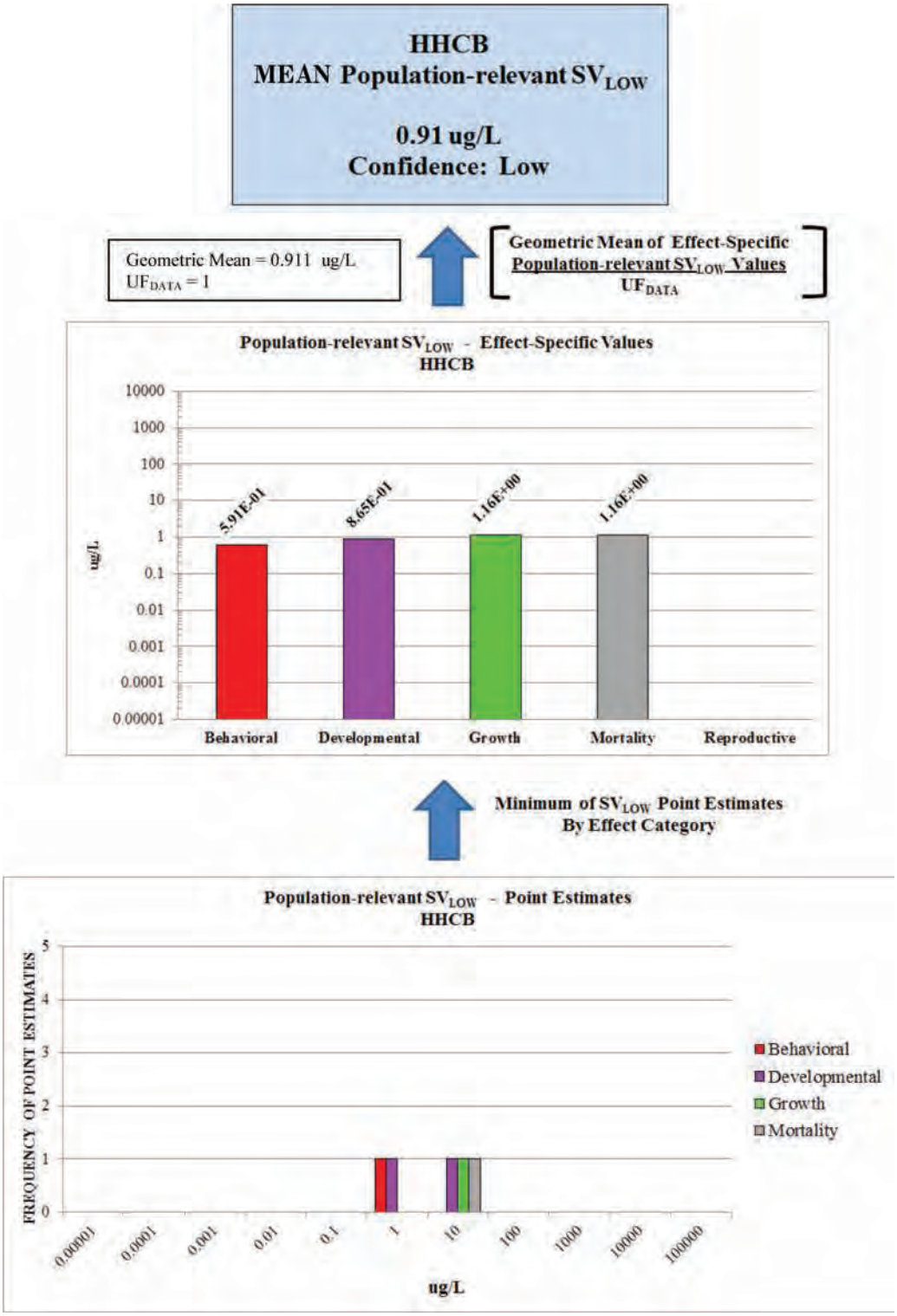
Effect Category	HHCB Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	36.8 (1)	0.591 (1)	34.5 (1)	0.237 (1)
Developmental	56.6 (1)	0.865 – 6.36 (2)	53.0 (1)	0.347 – 2.55 (2)
Growth	79.4 (1)	1.16 (1)	74.4 (1)	0.465 (1)
Mortality	79.4 (1)	1.16 (1)	74.4 (1)	0.465 (1)
Reproductive			3.26 (1)	0.0022 (1)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism			2.84 (1)	0.00192 (1)

4.4.8.3 SV Development: Graphics for HHCB

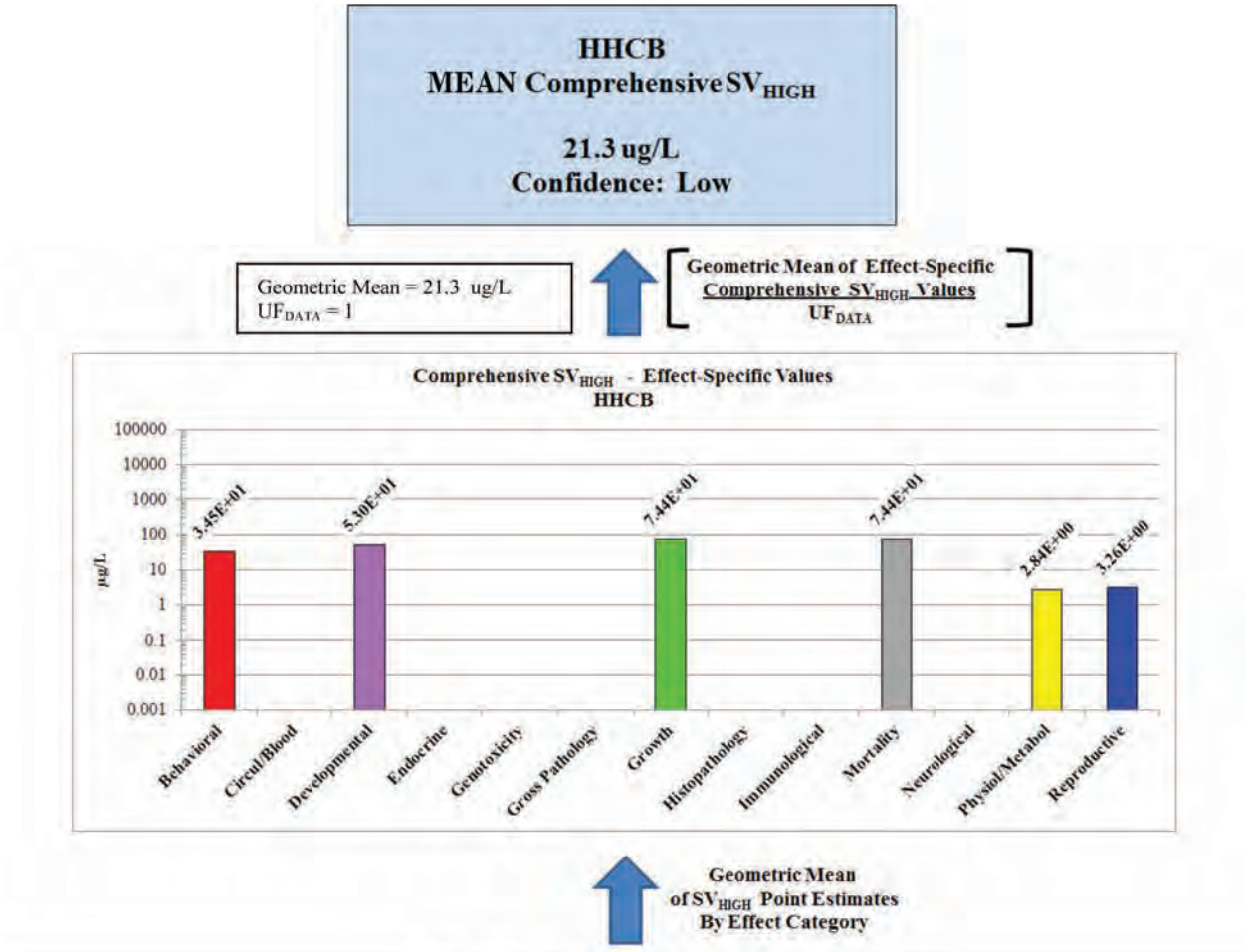
Population-relevant SV_{HIGH} Values for HHCB: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals

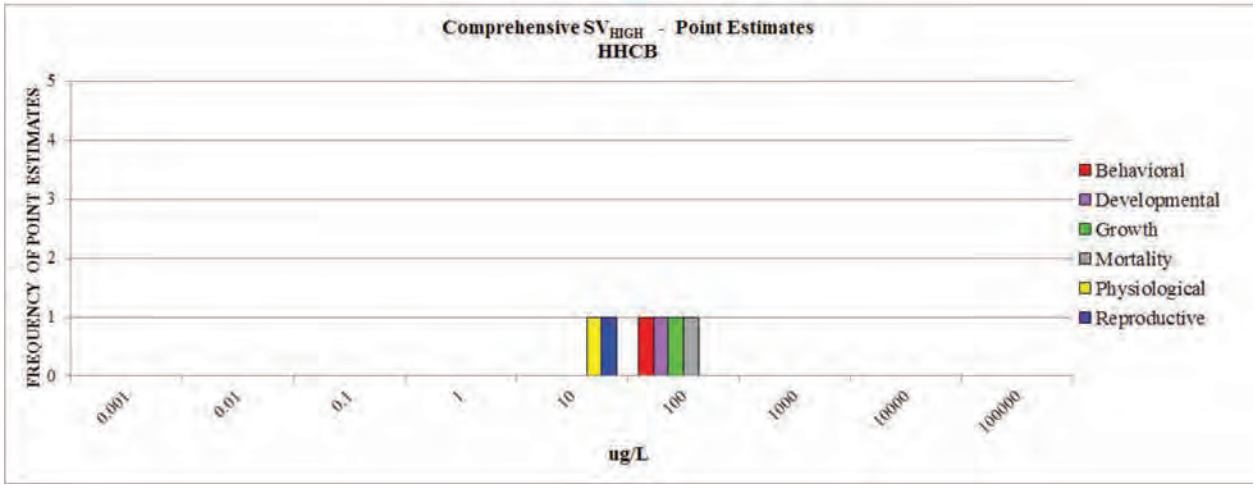


Population-relevant SV_{LOW} Values for HHCB: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

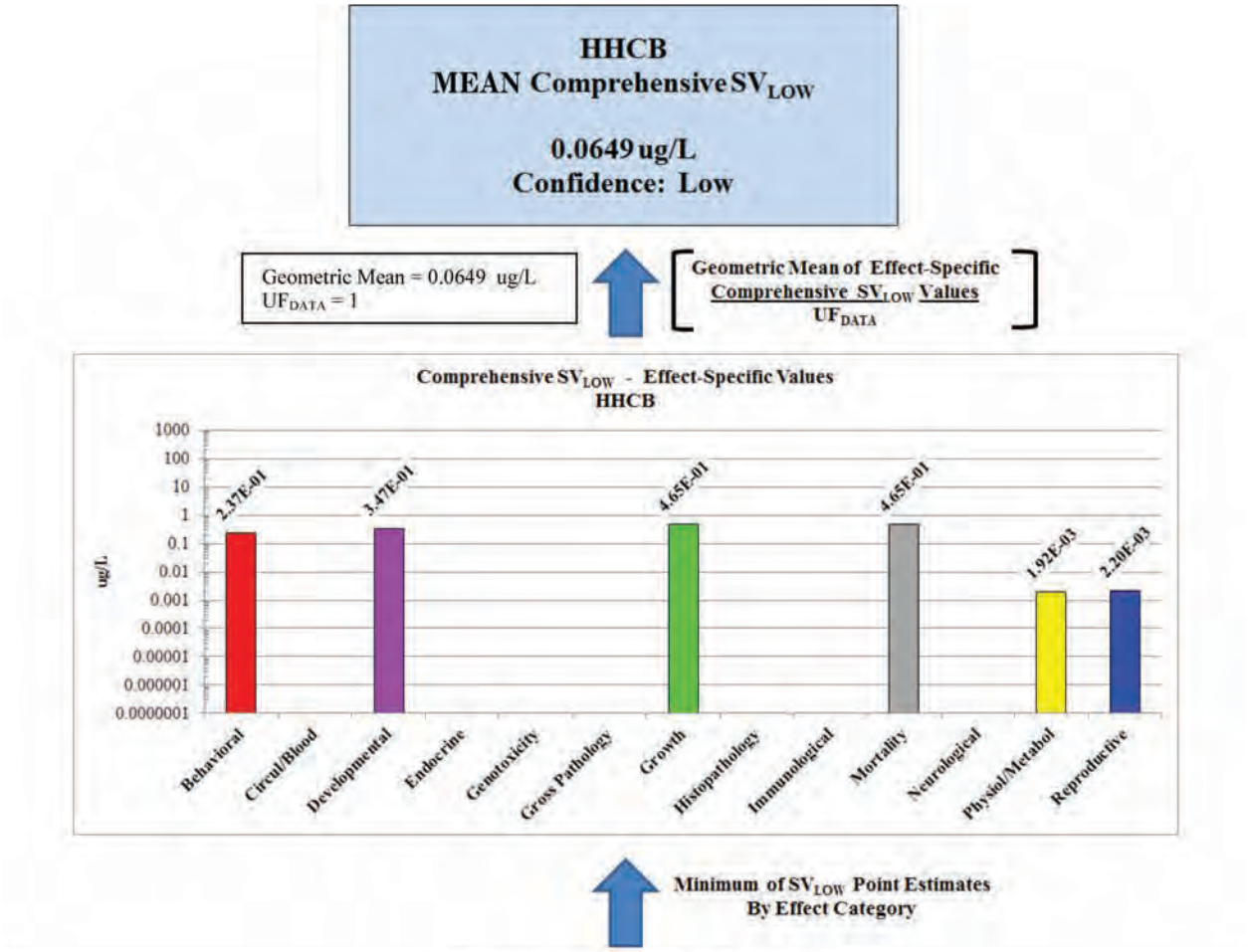


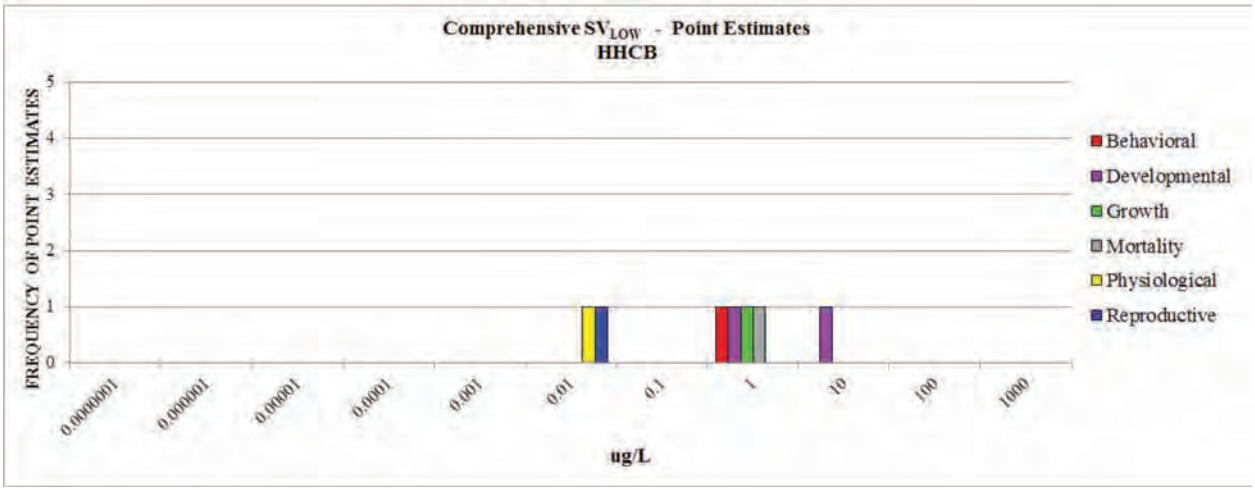
Comprehensive SV_{HIGH} Values for HHCB: Relationships among Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





Comprehensive SV_{LOW} Values for HHCB: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.9 Ibuprofen

4.4.9.1 Chemical Summary

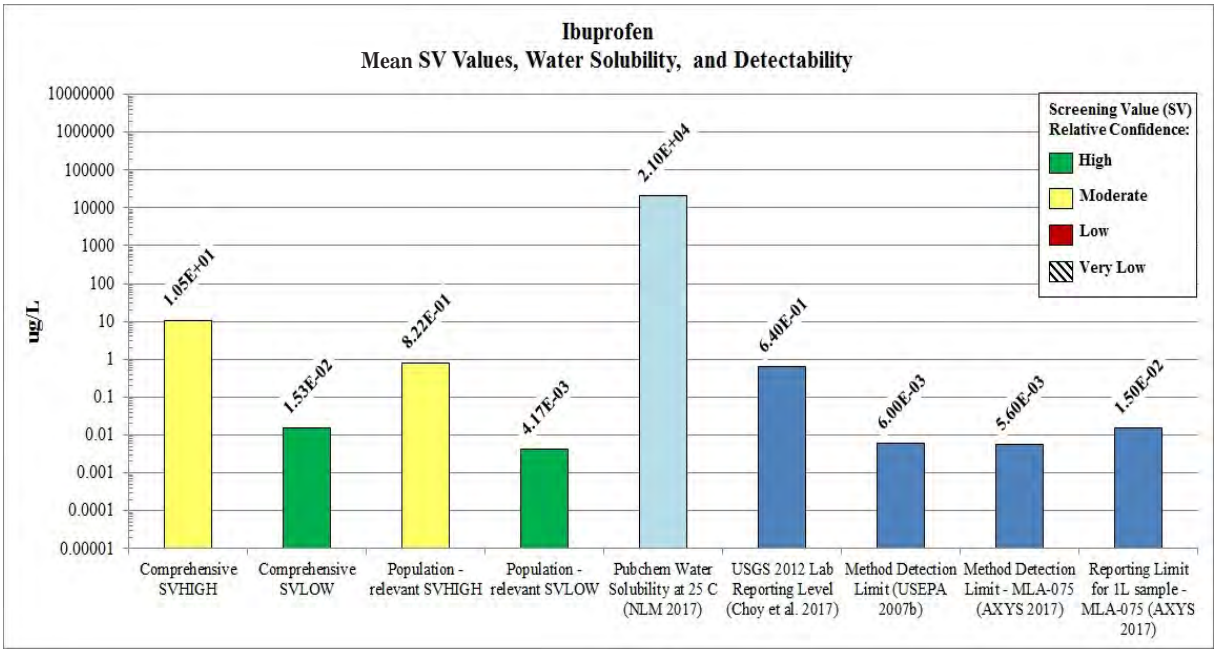
CEC Category: Pharmaceutical
CEC Subcategory: non-steroidal anti-inflammatory (NSAID), analgesic

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Ibuprofen is a commonly used nonsteroidal antiinflammatory (NSAID) drug which is available both by prescription and over-the-counter."
- *CAS Number:* 15687-27-1
- *Water Solubility:* 21 mg/l @ 25 deg C
- *logKow: 3.97*
- 2010-2012 USGS Laboratory Reporting *Level (Choy et al. 2017): 0.64 ug/L*
- *MDL – EPA Method 1694 (USEPA 2007b): 0.006 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.0056 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.015 ug/L*

4.4.9.2 Screening Value Summary

Mean SV Values (ug/L) for Ibuprofen



Mean Population-relevant SV$_{HIGH}$ for Ibuprofen: 0.822 µg/L

- *Relative Confidence:* Moderate. Three of the five population-relevant effect categories are represented, with 2 or more observations in each category.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Ibuprofen (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: common carp, Japanese medaka, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Flippin et al. 2007, Han et al. 2010, Islas-Flores et al. 2014, Ji et al. 2013, Morthorst et al. 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Developmental (2):* time to hatch, hatchability, fry survival, total number eggs, fertility, GSI, HSI, condition index, histopathology in gonads, liver, kidneys, malformation rates
    - *Mortality (3)*
    - *Reproductive (3):* GSI, reproductive hormone levels, time to hatch, hatchability, spawning frequency, number of spawning events, egg production per day, per week, and per spawn, rate of fertilization, egg diameter, total egg production
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Ibuprofen:* ranged from 2.5 to 7.4 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Ibuprofen:* 2

Mean Population-relevant SV$_{LOW}$ for Ibuprofen: 0.00417 µg/L

- *Relative Confidence:* High. All five population-relevant effect categories are represented, and four of the categories have at least 2 observations.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Ibuprofen (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: common carp, fathead minnow, Japanese medaka, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 6 studies published between 2007 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* unspecified endpoints
    - *Developmental (3):* time to hatch, hatchability, hatch success, fry survival, total number eggs, fertility, larval body length and weight, GSI, HSI, condition index, histopathology in gonads, liver, kidneys, malformation rates
    - *Growth (2):* overall body weights, condition factor
    - *Mortality (4)*
    - *Reproductive (3):* GSI, reproductive hormone levels, time to hatch, hatchability, spawning frequency, number of spawning events, egg production per day, per week, and per spawn, rate of fertilization, egg diameter, total egg production
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for Ibuprofen:* ranged from 78.6 to 786 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Ibuprofen:* 1

Mean Comprehensive SV$_{HIGH}$ for Ibuprofen: 105 µg/L

- *Relative Confidence:* Moderate. Although seven of the 13 effect categories have sufficient data to estimate a value, four of the categories have only one observation.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Ibuprofen (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: common carp, Indian major carp, Japanese medaka,

rainbow trout, zebrafish
- Life Stage(s): embryo, larva, juvenile, adult
- Publication(s): 8 studies published between 2007 and 2014
- Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Circulatory/Blood Constituents (1):* hemoglobin, hematocrit, RBS count, WBC count, mean cellular volume, mean cellular hemoglobin, plasma protein, plasma glucose
    - *Developmental (2):* time to hatch, hatchability, fry survival, total number eggs, fertility, GSI, HSI, condition index, histopathology in gonads, liver, kidneys, malformation rates
    - *Endocrine/Hormone (1):* plasma cortisol response to seawater exposure
    - *Genotoxicity (1):* COMET test, % apoptotic cells, RAPD-PCR test
    - *Mortality (3)*
    - *Physiology/Metabolism (1):* liver glycogen and liver glucose levels in multiple stressor test
    - *Reproductive (4):* GSI, reproductive hormone levels, time to hatch, hatchability, spawning frequency, number of spawning events, egg production per day, per week, and per spawn, rate of fertilization, egg diameter, total egg production

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for Ibuprofen:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Ibuprofen:* 1

<u>Mean Comprehensive SV$_{LOW}$ for Ibuprofen: 0.0153 µg/L</u>

- *Relative Confidence:* High. Relevant data were sufficient to generate 19 comprehensive type SV$_{LOW}$ point estimates, which are distributed among 10 of the 13 effect categories. Although six of the categories had only one observation each and none of the categories had more than four observations, the information was obtained from nine separate published sources on six different species of fish.

- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Ibuprofen (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*

    - Species: common carp, fathead minnow, Indian major carp, Japanese medaka, rainbow trout, zebrafish
    - Life Stage(s): embryo, larva, juvenile, adult
    - Publication(s): 9 studies published between 2007 and 2014
    - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
        - *Behavioral (1):* unspecified endpoints
        - *Circulatory/Blood Constituents (1):* hemoglobin, hematocrit, RBS count, WBC count, mean cellular volume, mean cellular hemoglobin, plasma protein, plasma glucose
        - *Developmental (3):* time to hatch, hatchability, hatch success, fry survival, total number eggs, fertility, larval body length and weight, GSI, HSI, condition index, histopathology in gonads, liver, kidneys, malformation rates
        - *Endocrine/Hormone (1):* plasma cortisol response to seawater exposure
        - *Genotoxicity (1):* COMET test, % apoptotic cells, RAPD-PCR test
        - *Growth (2)*
        - *Histopathology (1)*
        - *Mortality (4)*
        - *Physiology/Metabolism (1)*: liver glycogen and liver glucose levels in multiple stressor test
        - *Reproductive (4):* GSI, reproductive hormone levels, time to hatch, hatchability, spawning frequency, number of spawning events, egg production per day, per week, and per spawn, rate of fertilization, egg diameter, total egg production

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Ibuprofen: ranged from 196 to 1958 (see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Ibuprofen:* 1

Effect-Specific SV Values (ug/L) for Ibuprofen

- Population-relevant SV_{HIGH}: The ibuprofen effect-specific population-relevant SV_{HIGH} values range from 0.27 ug/L (Developmental) to 57.8 ug/L (Mortality) (Table 4-1a), although each effect category is represented by only one observation.

- Population-relevant SV_{LOW} : Available data were sufficient to estimate values for all five population-relevant effect categories, with effect-specific population-relevant SV_{LOW} values ranging from 0.0000636 ug/L (Developmental) to 8.65 (Behavioral) (Table 4-1b).

- Comprehensive SV_{HIGH} : Seven out of 13 effect categories had sufficient data to estimate effect-specific values, although four categories had only one observation. Effect-specific comprehensive SV_{HIGH} values range from 0.0126 ug/L (Genotoxicity) to 5,380 ug/L (Circulatory/ Blood Constituents) (Table 4-1c).

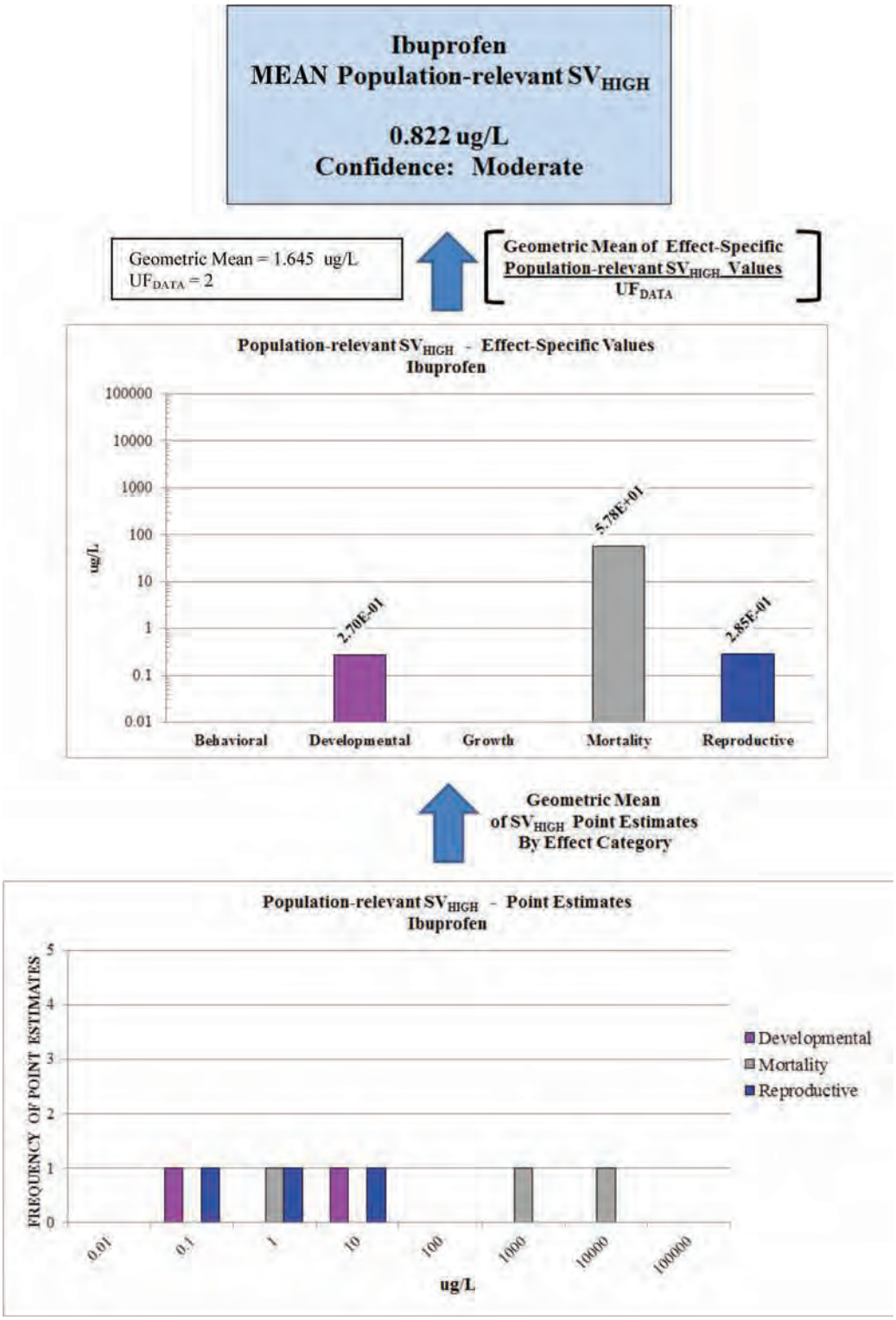
- Comprehensive SV_{LOW} : There were sufficient data to estimate values for 10 of the 13 effect categories, but there was only one observation in six of the categories. The effect-specific comprehensive SV_{LOW} values range from 0.0000255 ug/L (Developmental) to 14.5 ug/L (Circulatory/ Blood Constituents) (Table 4-1d).

SV Point Estimates for Ibuprofen

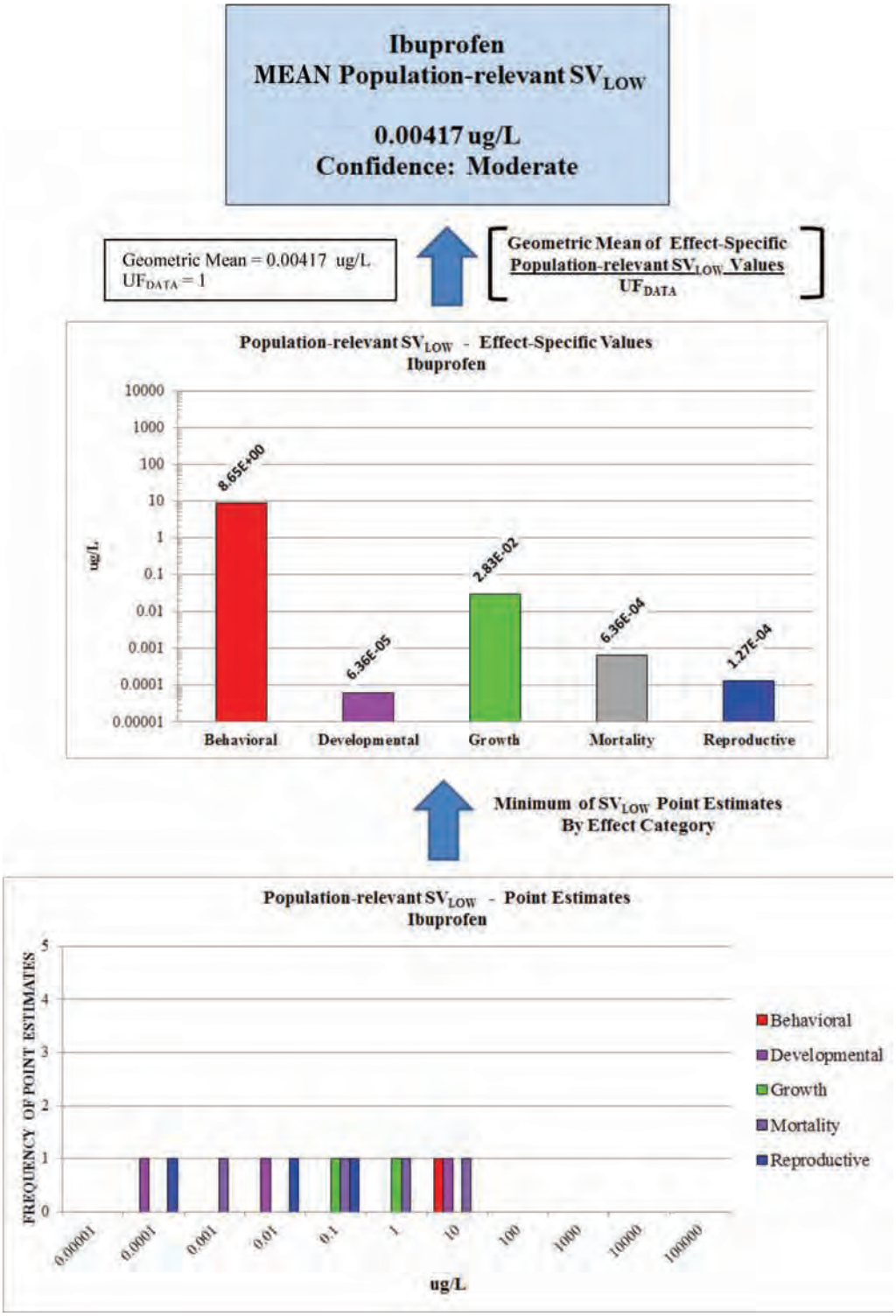
Effect Category	Ibuprofen Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral		8.65 (1)		3.47 (1)
Developmental	0.0404 – 1.8 (2)	0.0000636 – 8.65 (3)	0.0379 – 1.69 (2)	0.0000255 – 3.47 (3)
Growth		0.0283 – 2.15 (2)		0.011 – 0.861 (2)
Mortality	0.404 – 2370 (3)	0.000636 – 20.1 (4)	0.379 – 2222 (3)	0.000255 – 8.09 (4)
Reproductive	0.0202 – 2.83 (3)	0.000127 – 0.03 (3)	0.0189 – 2.65 (4)	0.0000511 – 0.119 (4)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents			5,379 (1)	14.5 (1)
Endocrine			189 (1)	0.511 (1)
Genotoxicity			0.0126 (1)	0.0000565 (1)
Gross Pathology				
Histopathology				0.255 (1)
Immunological				
Neurological				
Physiology/ Metabolism			189 (1)	0.511 (1)

4.4.9.3 SV Development: Graphics for Ibuprofen

Population-relevant SV_{HIGH} Values for Ibuprofen: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Population-relevant SV_{LOW} Values for Ibuprofen: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



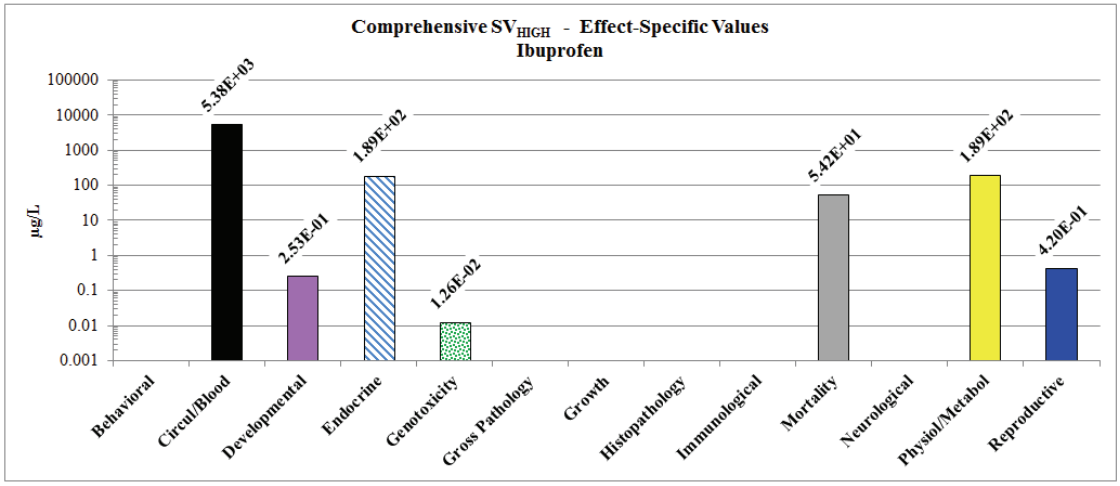
Comprehensive SV_{HIGH} Values for Ibuprofen: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

Ibuprofen
MEAN Comprehensive SV_{HIGH}

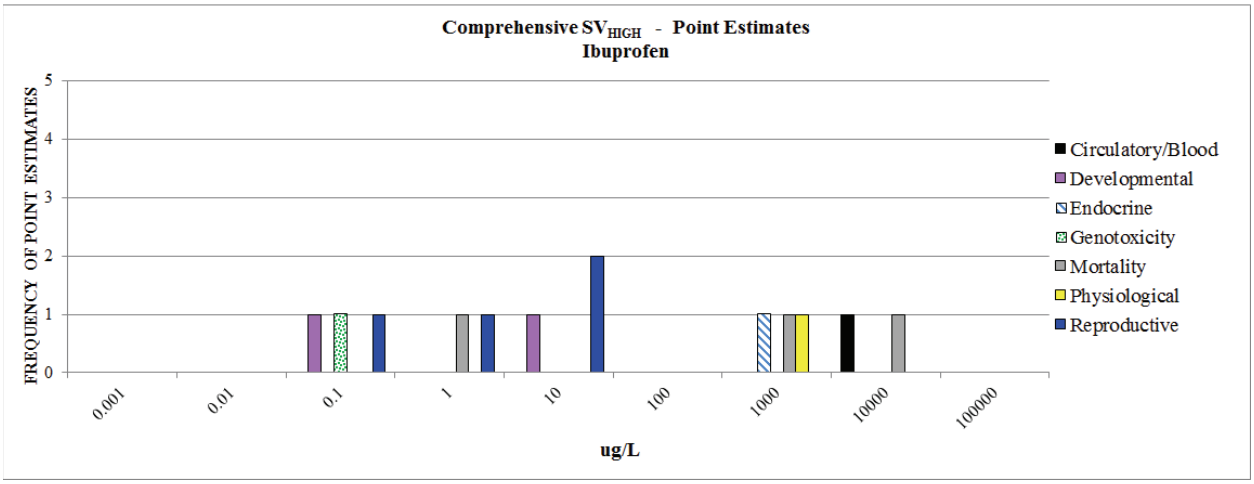
10.5 ug/L
Confidence: Moderate

Geometric Mean = 10.49 ug/L
UF_{DATA} = 1

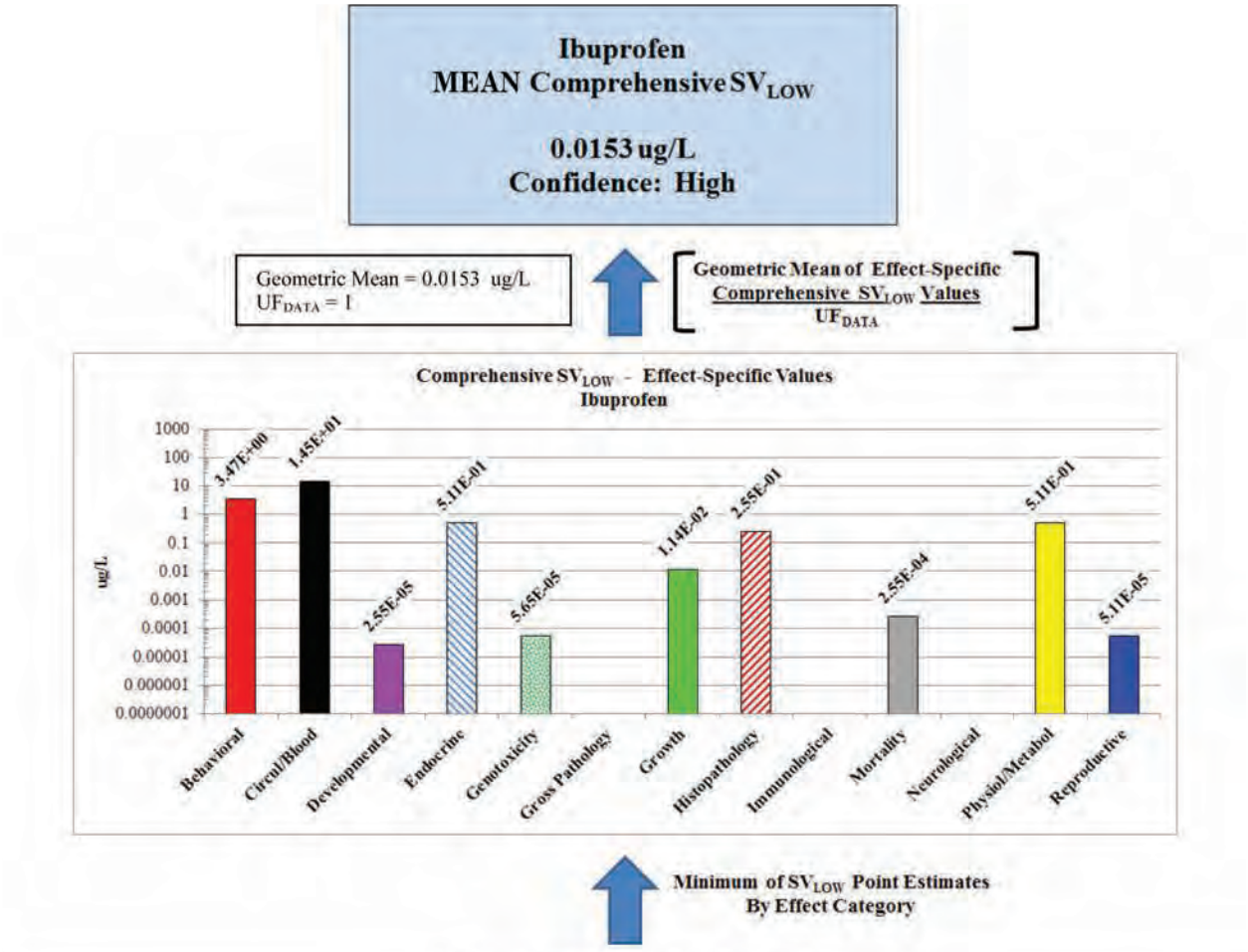
Geometric Mean of Effect-Specific Comprehensive SV_{HIGH} Values
UF_{DATA}

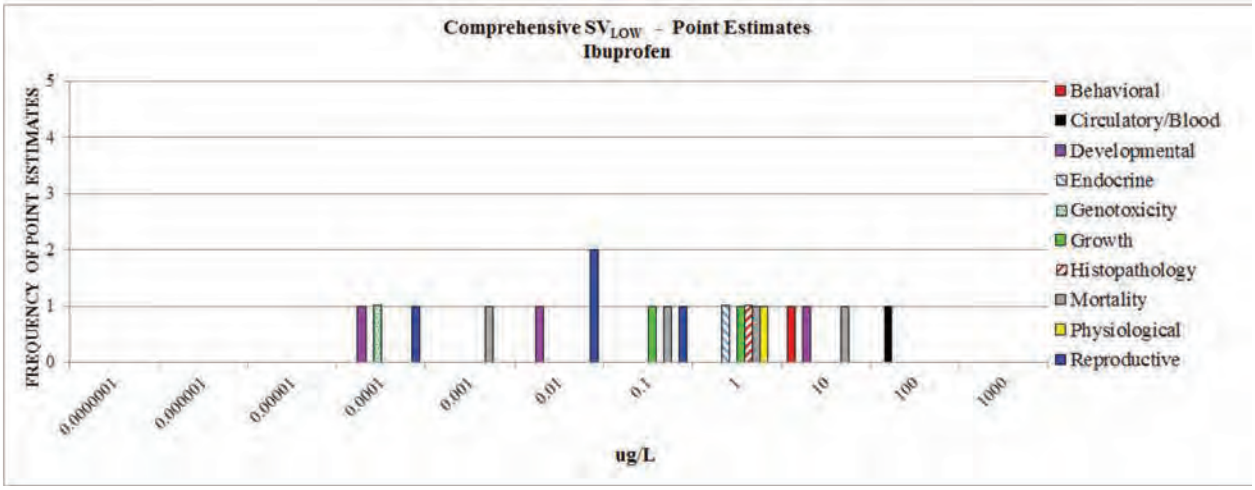


Geometric Mean of SV_{HIGH} Point Estimates By Effect Category



Comprehensive SV_{LOW} Values for Ibuprofen: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals





4.4.10 Lidocaine

4.4.10.1 Chemical Summary

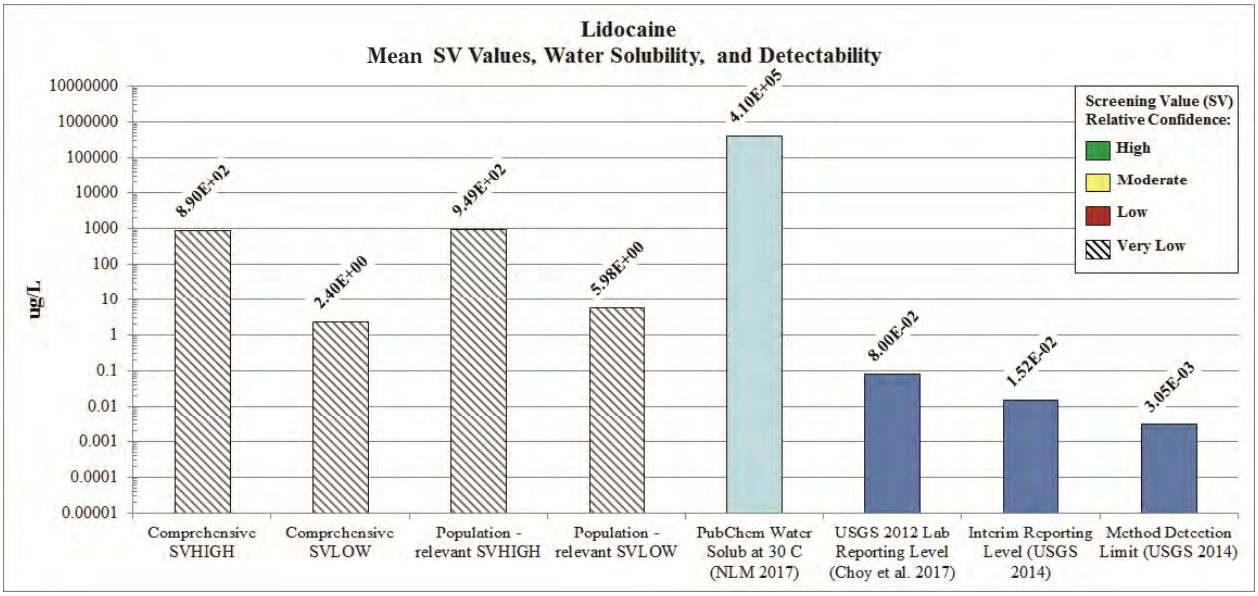
CEC Category: Pharmaceutical
CEC Subcategory: Antiarrhythmic

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Lidocaine is a local anesthetic and cardiac depressant used as an antiarrhythmia agent."
- *CAS Number:* 137-58-6
- *Water solubility:* 410 mg/L at 30 deg C
- *logKow:* 2.26 at pH 7.4
- *2010-2012 USGS Lab Reporting Level (Choy et al. 2017): 0.08 ug/L*
- *Interim Reporting Level – Techniques and Methods 5-B10 (USGS 2014): 0.0152 ug/L*
- *MDL – Techniques and Methods 5-B10 (USGS 2014): 0.00305 ug/L*

4.4.10.2 Screening Value Summary

Mean SV Values (ug/L) for Lidocaine



Mean Population-relevant SV$_{HIGH}$ for Lidocaine: 949 μg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category had sufficient data to estimate a value, and it was represented by only one observation.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Lidocaine (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: zebrafish
  - Life Stage(s): larva
  - Publication(s): Ellis and Soanes 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* larval activity levels, light-dark behavior test
- *Cumulative Uncertainty Factor applied to the LOAEC to obtain the Population-relevant SV$_{HIGH}$ point estimate for Lidocaine:* 2.475 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Lidocaine:* 5

Mean Population-relevant SV$_{LOW}$ for Lidocaine: 5.98 μg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category had sufficient data to estimate a value, and it was represented by only one observation.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Lidocaine (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: zebrafish
  - Life Stage(s): larva
  - Publication(s): Ellis and Soanes 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* larval activity levels, light-dark behavior test
- *Cumulative Uncertainty Factor applied to the Unbounded LOAEC to obtain a single Population-relevant SV$_{LOW}$ point estimate for Lidocaine: 393.1 (see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Lidocaine:* 5

Mean Comprehensive SV$_{HIGH}$ for Lidocaine: 890 μg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category had sufficient data to estimate a value, and it was represented by only one observation.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Lidocaine (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: zebrafish
  - Life Stage(s): larva
  - Publication(s): Ellis and Soanes 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* larval activity levels, light-dark behavior test
- *Cumulative Uncertainty Factor applied to the only LOAEC to obtain one Comprehensive SV$_{HIGH}$ point estimate for Lidocaine:* 2.64 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Lidocaine:* 5

Mean Comprehensive SV$_{LOW}$ for Lidocaine: 2.4 μg/L

- *Relative Confidence:* Very Low. Only the Behavioral effect category had sufficient data to estimate a value, and it was represented by only one observation.
- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Lidocaine (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: zebrafish
  - Life Stage(s): larva
  - Publication(s): Ellis and Soanes 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* larval activity levels, light-dark behavior test
- *Cumulative Uncertainty Factor applied to the single NOAEC to obtain the Comprehensive SV$_{LOW}$ point estimate for Lidocaine:* 979 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Lidocaine:* 5

Effect-Specific SV Values (ug/L) for Lidocaine

- Population-relevant SV_{HIGH}: The only lidocaine effect-specific population-relevant SV_{HIGH} value was 4,750 ug/L for Behavioral effects (Table 4-1a), based on only one observation.

- Population-relevant SV_{LOW} : The only effect-specific population-relevant SV_{LOW} value was 12 ug/L for Behavioral effects (Table 4-1b), based on only one observation.

- Comprehensive SV_{HIGH} : The only effect-specific comprehensive SV_{HIGH} value was 4,450 ug/L for Behavioral effects (Table 4-1c), based on only one observation.

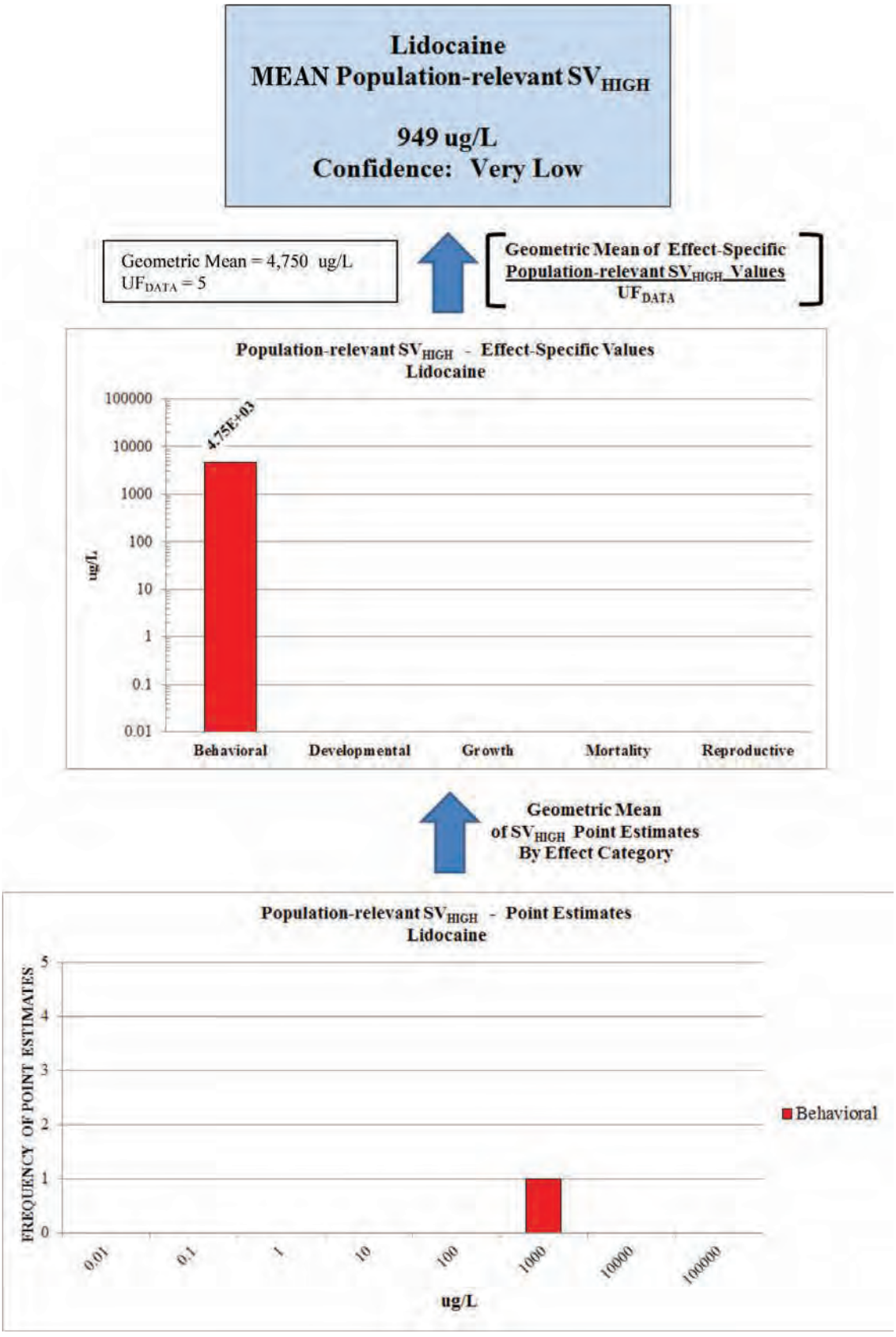
- Comprehensive SV_{LOW} : The only effect-specific comprehensive SV_{LOW} value was 12 ug/L for Behavioral effects (Table 4-1d), based on only one observation.

SV Point Estimates for Lidocaine

Effect Category	Lidocaine Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	4747 (1)	29.9 (1)	4451 (1)	12 (1)
Developmental				
Growth				
Mortality				
Reproductive				
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.10.3 SV Development: Graphics for Lidocaine

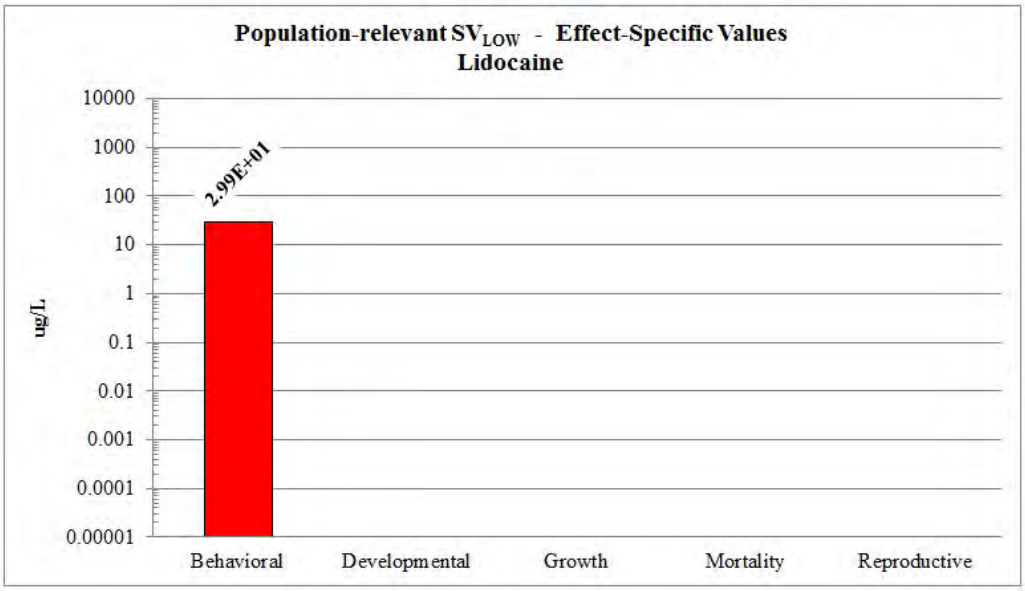
Population-relevant SV_{HIGH} Values for Lidocaine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



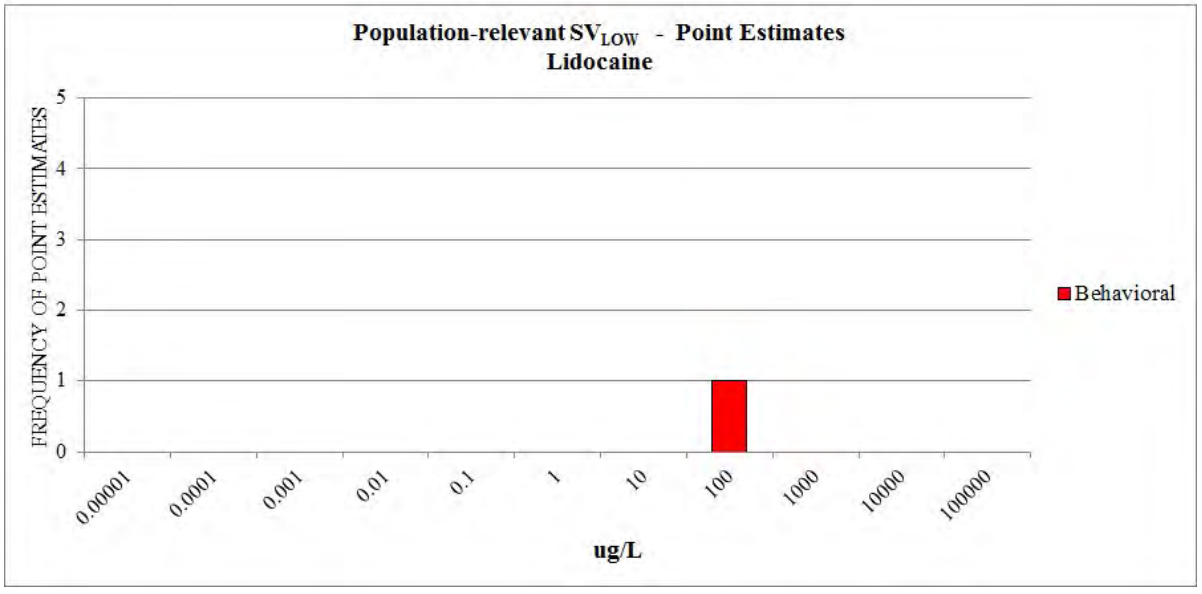
Population-relevant SV_{LOW} Values for Lidocaine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

Geometric Mean = 29.9 ug/L
UF_{DATA} = 5

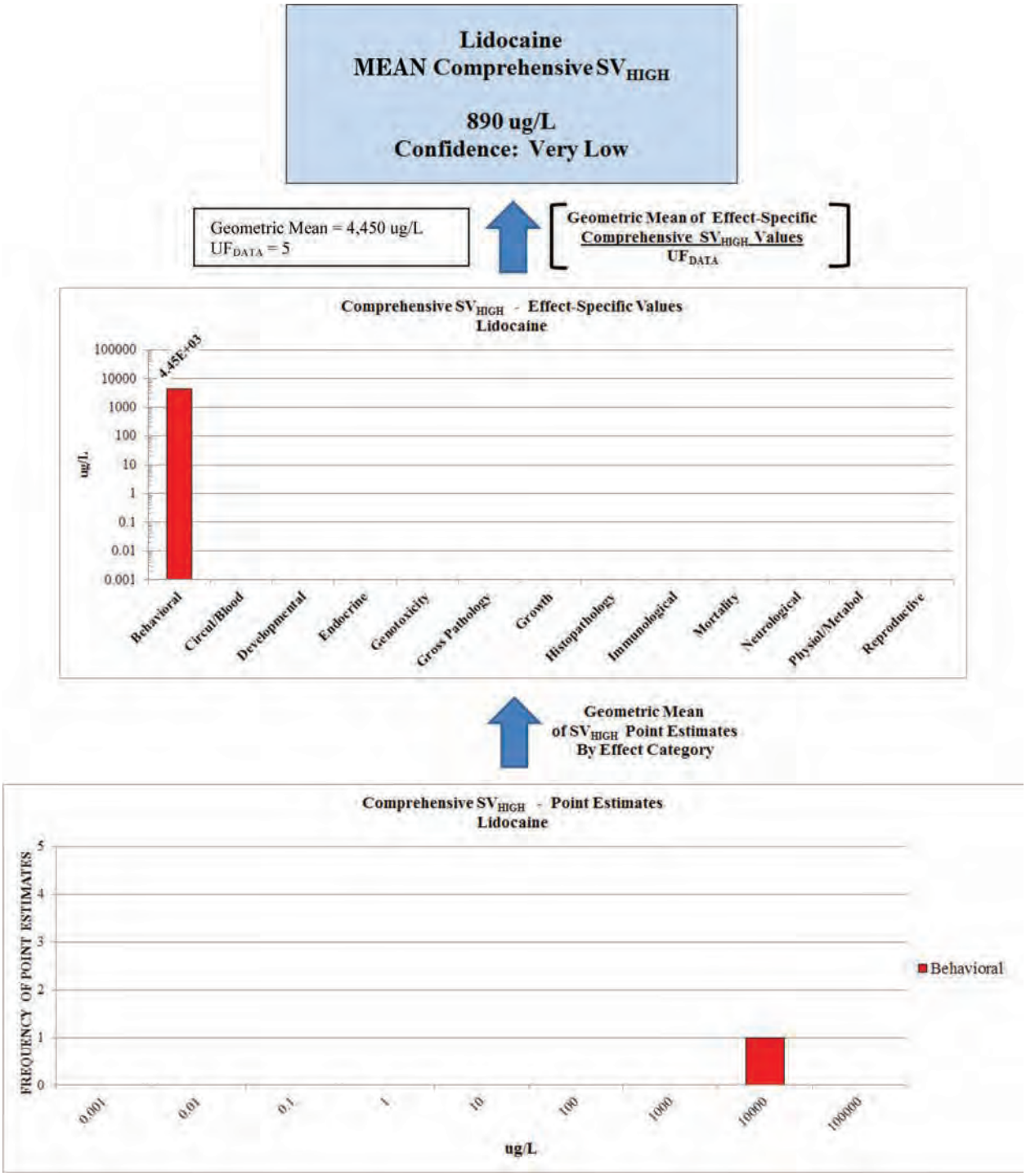
Geometric Mean of Effect-Specific Population-relevant SV_{LOW} Values
UF_{DATA}



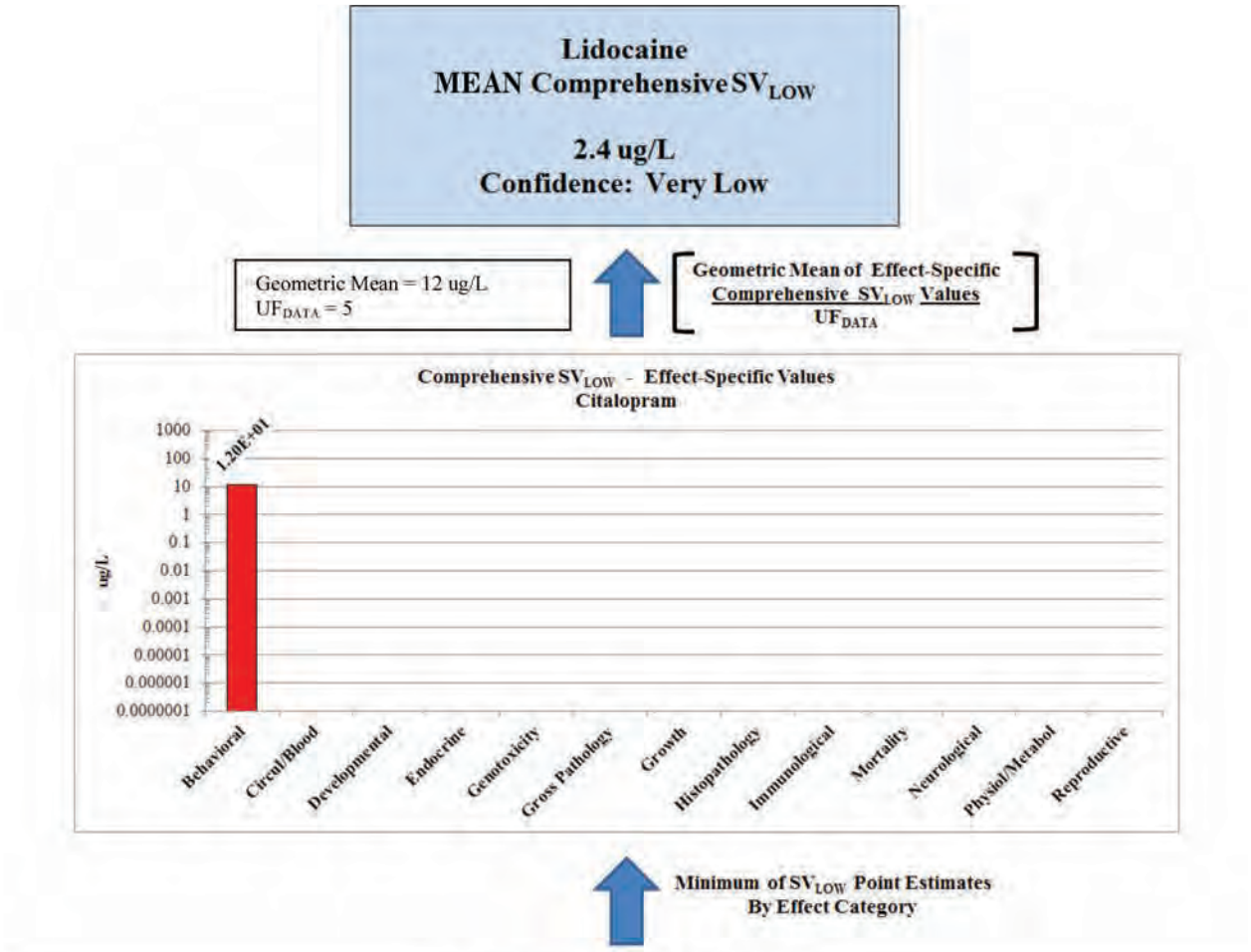
Minimum of SV_{LOW} Point Estimates By Effect Category

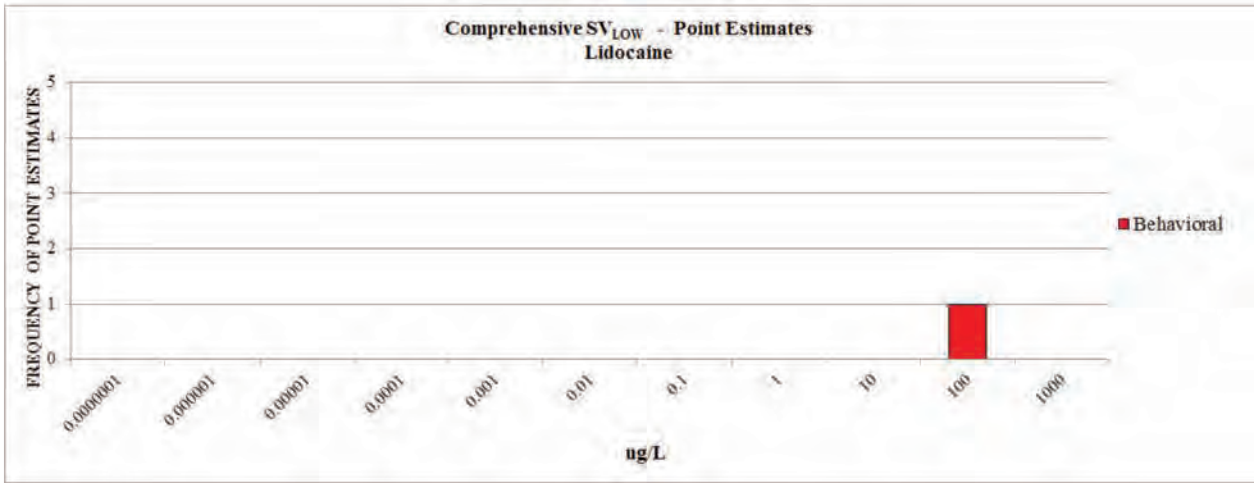


Comprehensive SV_{HIGH} Values for Lidocaine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Lidocaine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.11 β-Sitosterol

4.4.11.1 Chemical Summary

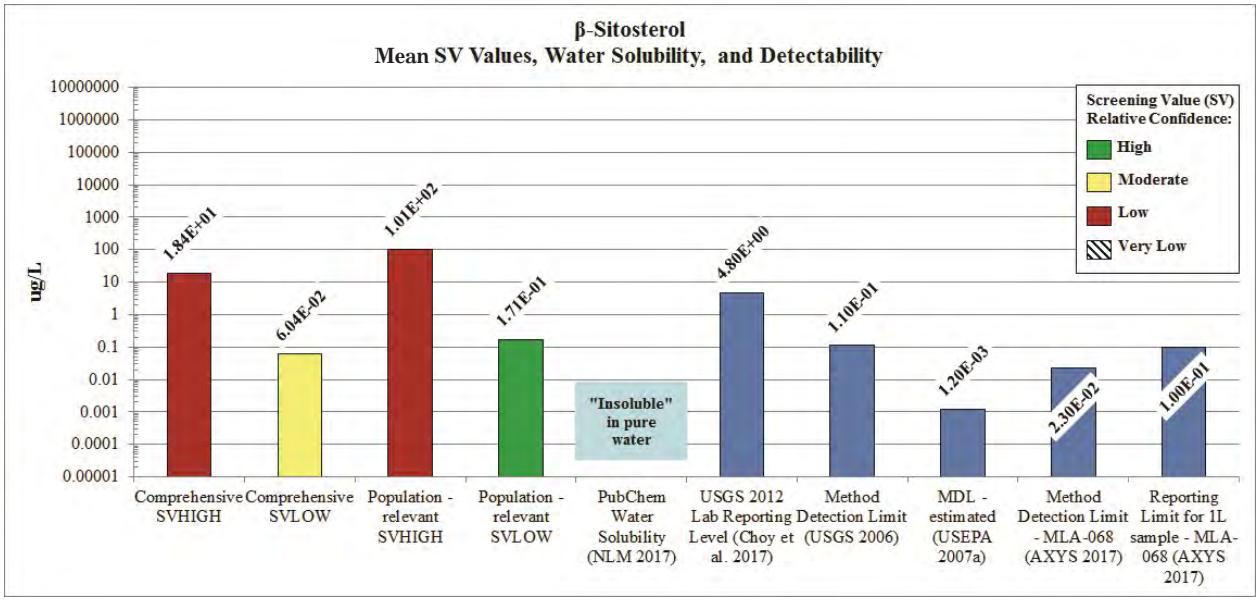
CEC Category: Hormone
CEC Subcategories: Plant hormone, phytosterol

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "Beta-Sitosterol, a main dietary phytosterol found in plants…. Phytosterols are plant sterols found in foods such as oils, nuts and vegetables."
- *CAS Number:* 83-46-5
- *Water Solubility:* insoluble in pure water
- *logKow:* 9.65 (Choy et al. 2017)
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 4.8 ug/L*
- *MDL – Techniques and Methods 5-B4 (USGS 2006): 0.11 ug/L*
- *MDL (estimated) – EPA Method 1698 (USEPA 2007a): 0.0012 ug/L*
- *MDL – AXYS Method MLA-068 (AXYS 2017): 0.023 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-068 (AXYS 2017): 0.1 ug/L*

4.4.11.2 Screening Value Summary

Mean SV Values (ug/L) for β-Sitosterol



Mean Population-relevant SV$_{HIGH}$ for β-Sitosterol : 101 μg/L

- *Relative Confidence:* Low. Only two of the five population-relevant effect categories are represented (Behavioral and Developmental), and only one category has more than two point estimate observations.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for β-Sitosterol (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: Beta fish, flagfish, Japanese medaka, rainbow trout, Siamese fighting fish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Brown et al. 2014, Clotfelter and Rodriquez 2006, Orrego et al. 2011
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (2):* male nest building success, nest size, spontaneous swimming, aggressiveness, female reproductive behavior
    - *Developmental (3):* time to hatch, egg mortality, hatchability, embryo survival, prevalence embryo abnormalities, larval/juvenile survival and sex ratio
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for β-Sitosterol:* ranged from 2.5 to 5 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for β-Sitosterol:* 2

Mean Population-relevant SV$_{LOW}$ for β-Sitosterol: 0.171 μg/L

- *Relative Confidence:* High. All five population-relevant effect categories are represented, three of the categories have at least three observations, and data from six fish species were included in this estimate.
- R*epresentation in the Population-relevant SV$_{LOW}$ Dataset for β-Sitosterol (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: Beta fish, flagfish, Japanese medaka, rainbow trout, Siamese fighting fish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 7 studies published between 1998 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (2):* male nest building success, nest size, spontaneous swimming, aggressiveness, female reproductive behavior
    - *Developmental (4):* time to hatch, egg mortality, hatchability, percent hatch, embryo survival, prevalence embryo abnormalities, larval/juvenile survival and sex ratio, larval growth
    - *Growth (3):* weight, length, condition factor
    - *Mortality (1)*
    - *Reproductive (5):* sperm concentration, motility and velocity, fertilization success, GSI, oocyte histology, oocyte maturation, sex ratio, reproductive hormone levels, total number of eggs, egg diameter, number eggs/female/day, total number of spawns, tubercle formation in males
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for β-Sitosterol:* ranged from 78.6 to 786 (see Attachment 4-2B for breakdown of the component UF values by SV point estimate)
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for β-Sitosterol:* 1

Mean Comprehensive SV$_{HIGH}$ for β-Sitosterol: 18.4 μg/L

- *Relative Confidence:* Low. Only four of 13 effect categories are represented.

- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for β-Sitosterol (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: Beta fish, flagfish, goldfish, Japanese medaka, rainbow trout, Siamese fighting fish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 6 studies published between 1997 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (2):* male nest building success, nest size, spontaneous swimming, aggressiveness, female reproductive behavior
    - *Circulatory/Blood Constituents (2):* plasma total cholesterol
    - *Developmental (3):* time to hatch, egg mortality, hatchability, embryo survival, prevalence embryo abnormalities, larval/juvenile survival and sex ratio
    - *Reproductive (4):* reproductive hormone levels, GSI, sex ratio

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for β-Sitosterol:* ranged from 2.6 to 5.3 (see Attachment 4-2C for breakdown of component UF values by SV point estimate)

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for β-Sitosterol:* 3

<u>Mean Comprehensive SV$_{LOW}$ for β-Sitosterol: 0.0604 μg/L</u>

- *Relative Confidence:* Moderate. Six of 13 effect categories are represented, but two of the categories have two or fewer observations.

- *Representation in the Comprehensive SV$_{LOW}$ Dataset for β-Sitosterol (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: Beta fish, fathead minnow, flagfish, goldfish, Japanese medaka, rainbow trout, Siamese fighting fish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 8 studies published between 1997 and 2014
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (5):* male nest building success, nest size, spontaneous swimming, aggressiveness, female reproductive behavior, timing of swim-up
    - *Circulatory/Blood Constituents (2):* plasma total cholesterol
    - *Developmental (4):* time to hatch, egg mortality, hatchability, percent hatch, embryo survival, prevalence embryo abnormalities, larval/juvenile survival and sex ratio, larval growth
    - *Growth (3):* weight, length, condition factor
    - *Mortality (1)*
    - *Reproductive (8):* sperm concentration, motility and velocity, fertilization success, GSI, oocyte histology, oocyte maturation, sex ratio, reproductive hormone levels, total number of eggs, egg diameter, number eggs/female/day, total number of spawns, tubercle formation in males

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for β-Sitosterol:* ranged from 196 to 1958 (see Attachment 4-2D for breakdown of the component UF values by SV point estimate)

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for β-Sitosterol:* 1

Effect-Specific SV Values (ug/L) for β-Sitosterol

• Population-relevant SV_{HIGH}: Theβ-sitosterol effect-specific population-relevant SV_{HIGH} values range from 2.02 ug/L (Behavioral) to 2,020 ug/L (Developmental) (Table 4-1a).

• Population-relevant SV_{LOW}: Available data were sufficient to estimate values for all five population-relevant effect categories, with effect-specific population-relevant SV_{LOW} values ranging from 0.00318 ug/L (Behavioral and Reproductive) to 9.48 (Developmental) (Table 4-1b).

• Comprehensive SV_{HIGH} : Four out of 13 effect categories had sufficient data to estimate effect-specific values, which range from 14.2 ug/L (Circulatory/ Blood Constituents) to 1,890 ug/L (Developmental) (Table 4-1c).

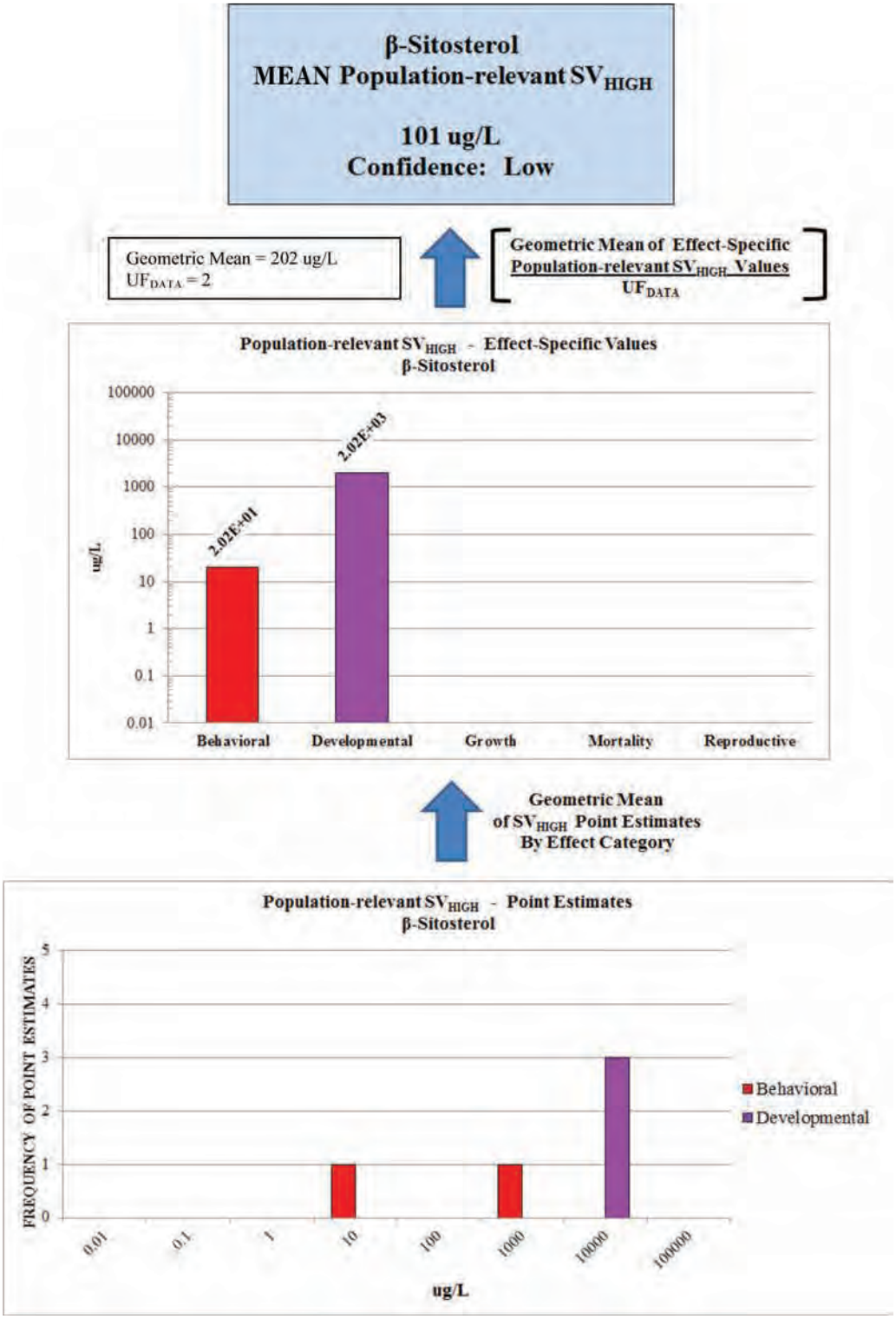
• Comprehensive SV_{LOW} : There were sufficient data to estimate values for six of the 13 effect categories, with values ranging from 0.00128 ug/L (Behavioral) to 3.8 ug/L (Developmental) (Table 4-1d).

SV Point Estimates for β-Sitosterol

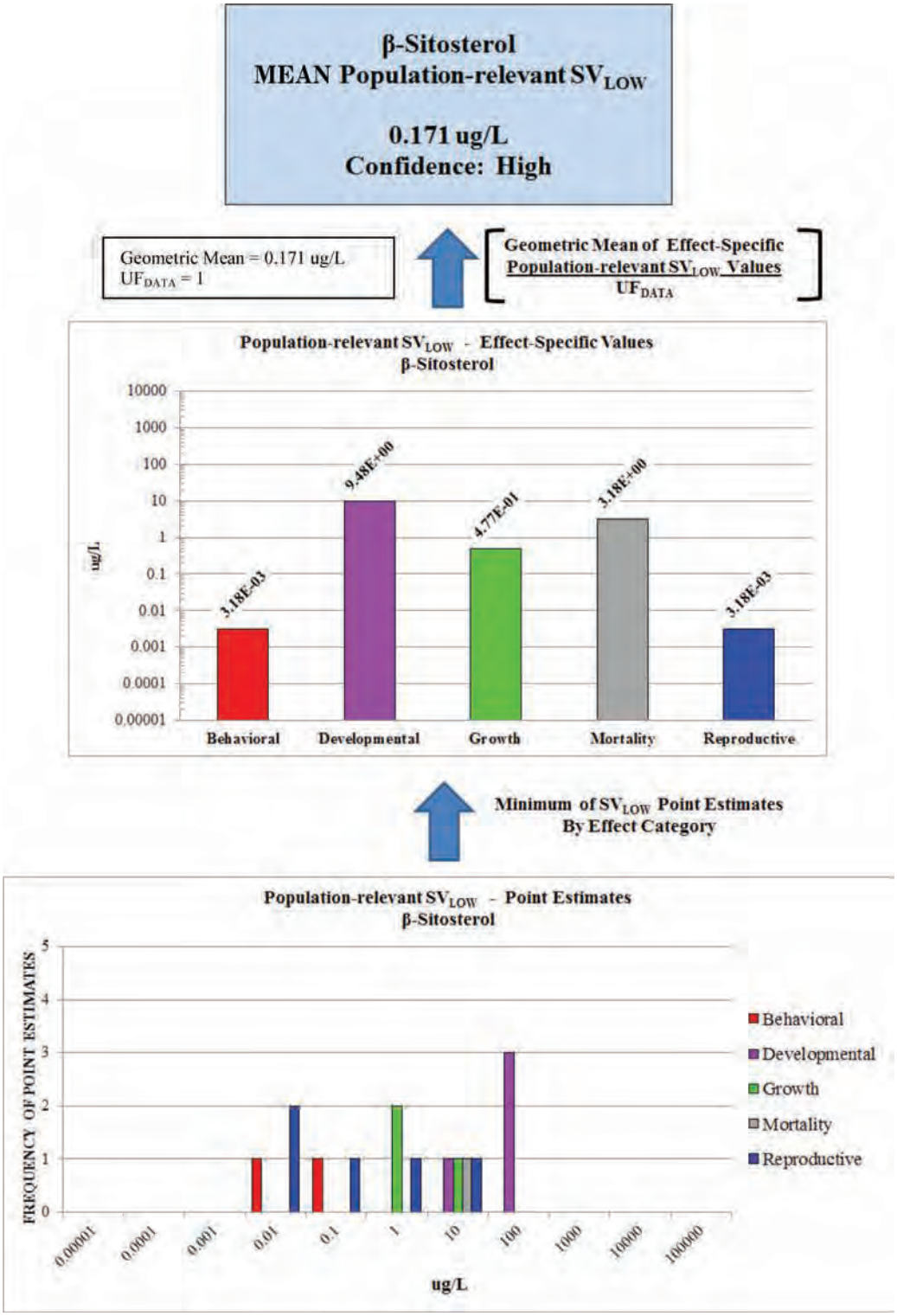
Effect Category	**β-Sitosterol Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category**			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	2.02 – 202 (2)	0.00318 – 0.0127 (2)	1.9 – 189 (2)	0.00128 – 12.8 (5)
Developmental	2020 (3)	9.48– 12.7 (4)	1894 (3)	3.8 – 5.1 (4)
Growth		0.477 – 9.48 (3)		0.192 – 3.8 (3)
Mortality		3.18 (1)		1.28 (1)
Reproductive		0.00318 – 9.48 (5)	4.73 – 56.8 (4)	0.00128 – 3.8 (8)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents			14.2 (2)	0.0319 – 0.0383 (2)
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.11.3 SV Development: Graphics for β-Sitosterol

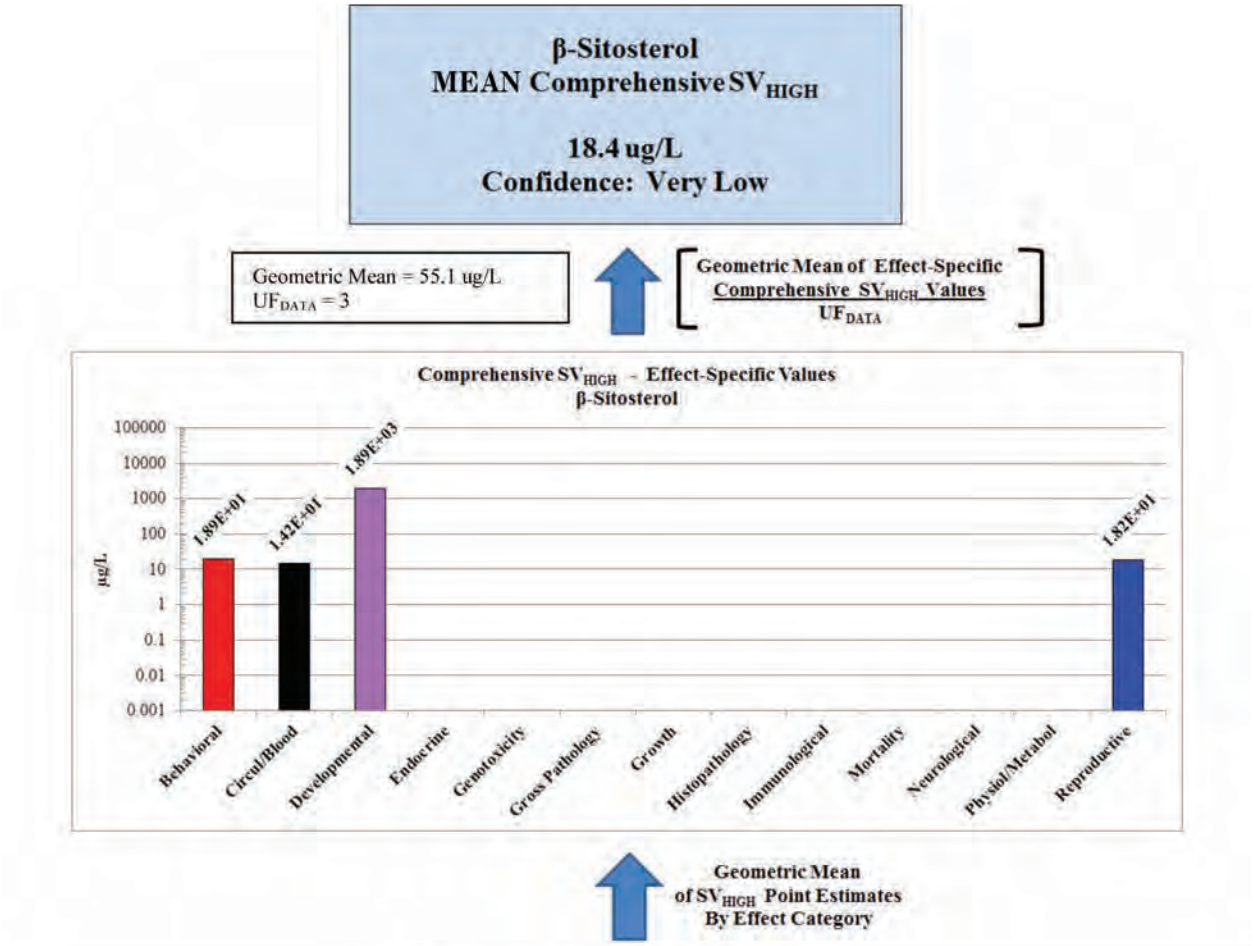
Population-relevant SV_{HIGH} Values for β-Sitosterol: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

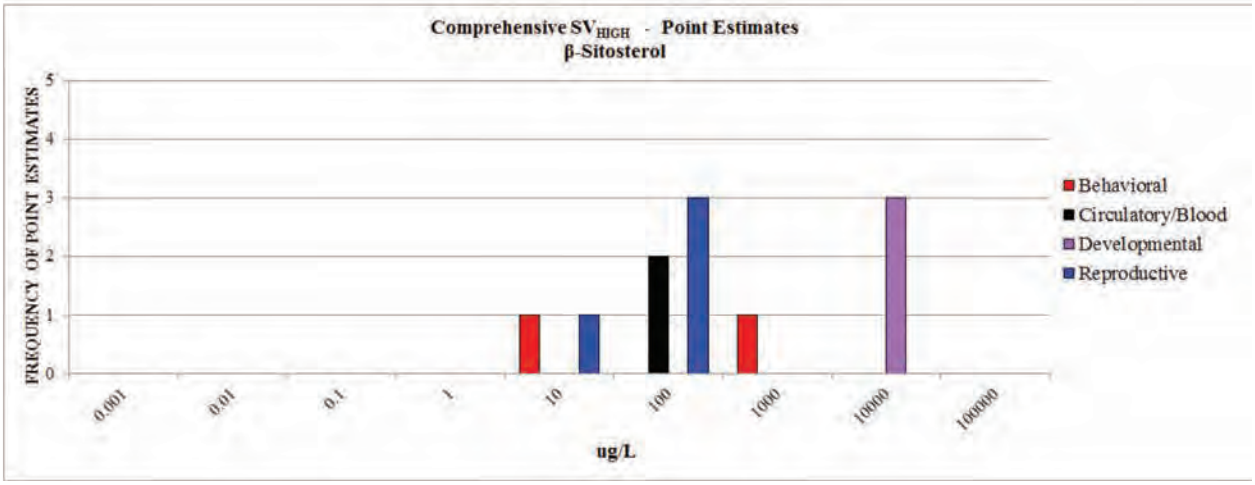


Population-relevant SV_{LOW} Values for β-Sitosterol: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

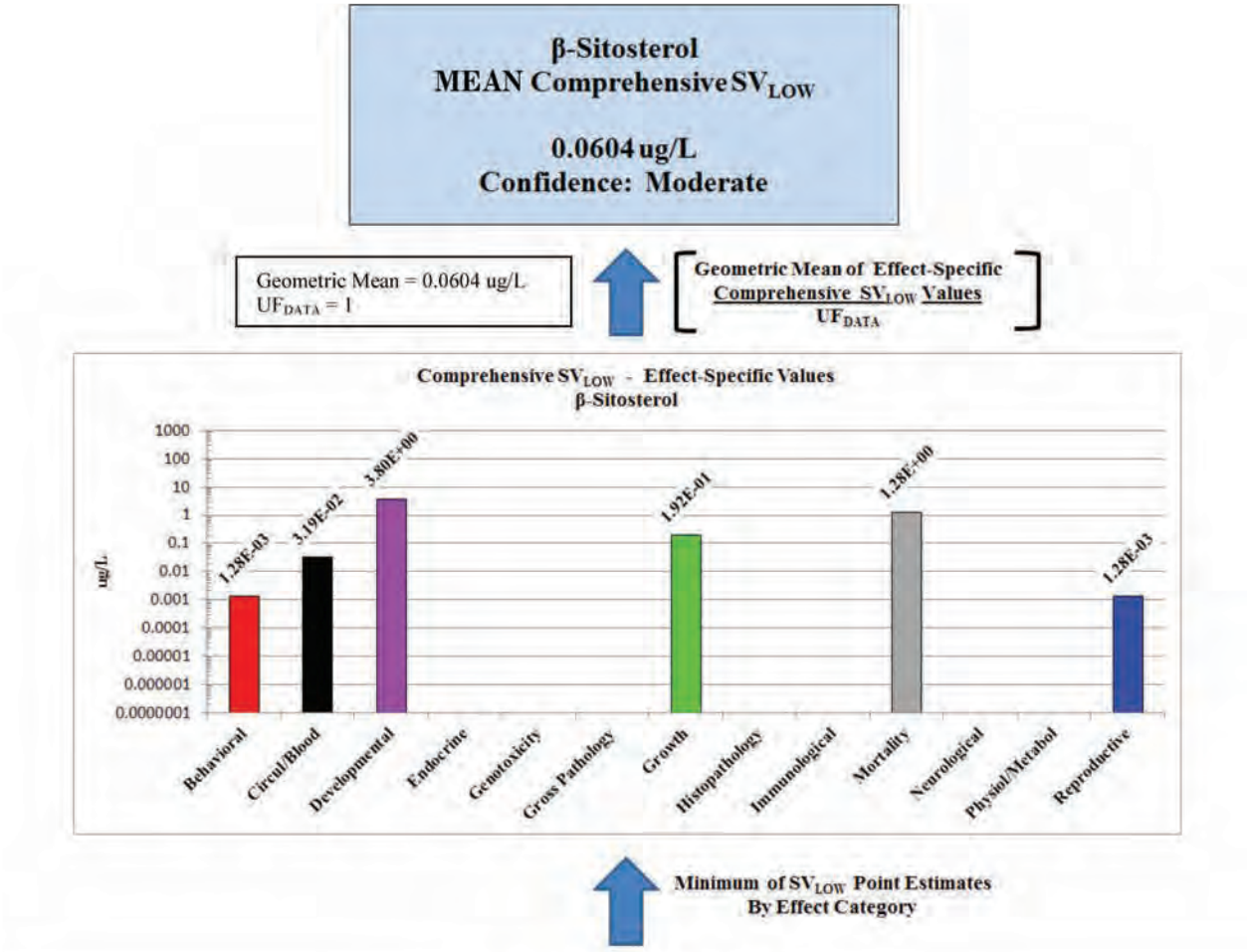


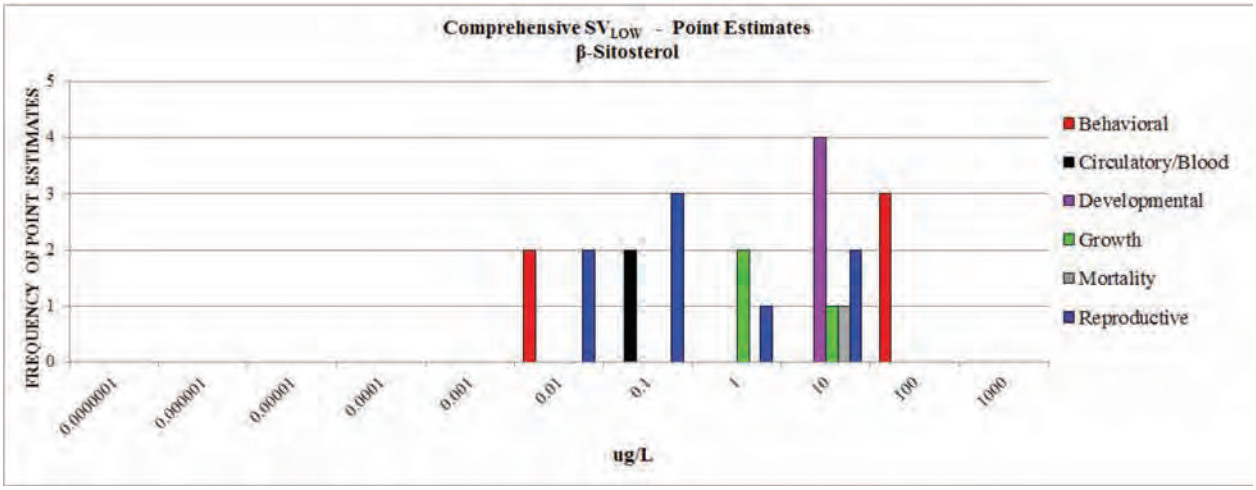
Comprehensive SV_{HIGH} Values for β-Sitosterol: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





Comprehensive SV_{LOW} Values for β-Sitosterol: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.12 Tris(2-butoxyethyl) phosphate (TBEP)

4.4.12.1 Chemical Summary

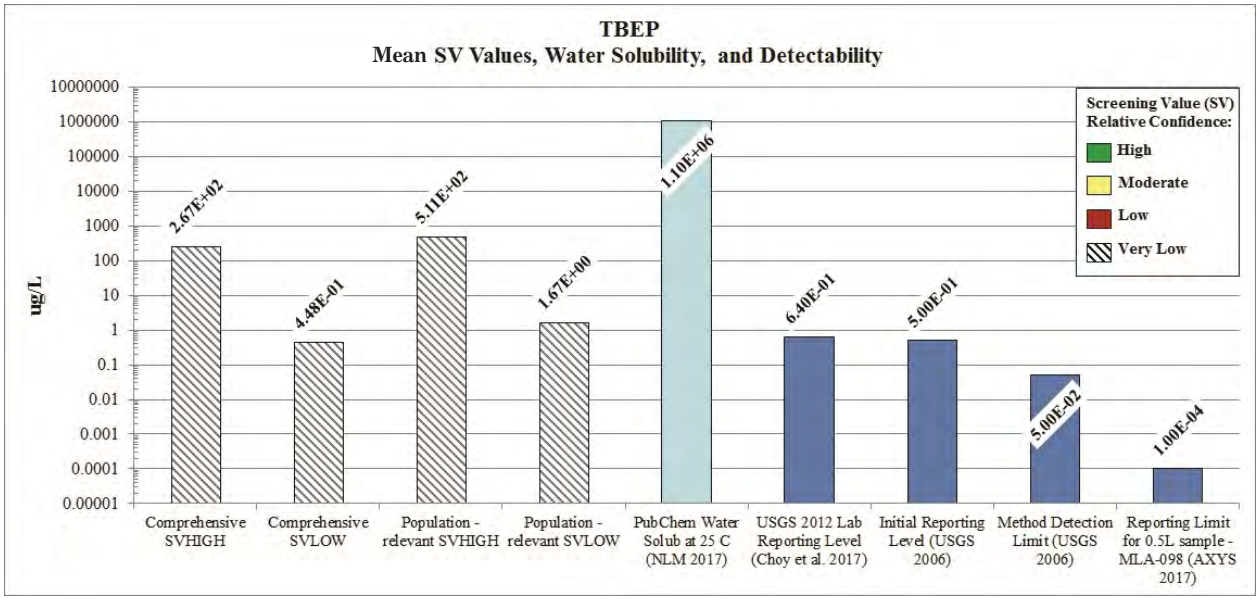
CEC Category: Flame retardant

The following chemical information was obtained from the PubChem database (NLM 2016), unless otherwise indicated:

- *Usage:* "Phosphate ester flame retardants are human-made chemicals added to consumer and industrial products for the purpose of reducing flammability."
- *CAS Number:* 78-51-3
- *Water Solubility:* 1,100 mg/L at 25 deg C
- *logKow:* 3.75
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 0.64 ug/L*
- *Reporting Level - Techniques and Methods 5-B4 (USGS 2006): 0.5 ug/L*
- *MDL – Techniques and Methods 5-B4 (USGS 2006): 0.05 ug/L*
- *Reporting Limit for 0.5L sample – AXYS Method MLA-098 (AXYS 2017): 0.0001 ug/L*

4.4.12.2 Screening Value Summary

Mean SV Values (ug/L) for TBEP



Mean Population-relevant SV$_{HIGH}$ for TBEP: 511 µg/L

- *Relative Confidence:* Very Low. Only three of the five population-relevant effect categories are represented, with two of the categories having only 1 SV point estimate each.

- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for TBEP (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo
  - Publication(s): Han et al. 2014, Springborn Bionomics, Inc. 1984
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* equilibrium
    - *Developmental (2):* embryo heart rate, body weight, survival, and hatch rate
    - *Mortality (1)*

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for TBEP:* ranged from 2.5 to 7.4 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for TBEP:* 2

Mean Population-relevant SV$_{LOW}$ for TBEP: 1.67 µg/L

- *Relative Confidence.* Very Low. Only three of the five population-relevant effect categories are represented, with two of the categories having only 1 SV point estimate each.

- *Representation in the Population-relevant SV$_{LOW}$ Dataset for TBEP (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo
  - Publication(s): Han et al. 2014, Springborn Bionomics, Inc. 1984
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (1):* equilibrium
    - *Developmental (2):* embryo heart rate, body weight, survival, and hatch rate
    - *Mortality (1)*

- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for TBEP:* ranged from 157 to 1179 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for TBEP:* 2

Mean Comprehensive SV$_{HIGH}$ for TBEP: 267 µg/L

- *Relative Confidence:* Very Low. Only three of the 13 effect categories are represented, with two of the categories having only 1 SV point estimate each.

- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for TBEP (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo
  - Publication(s): Han et al. 2014, Springborn Bionomics, Inc. 1984
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* equilibrium
    - *Developmental (2):* embryo heart rate, body weight, survival, and hatch rate, apoptosis in tail
  - *Mortality (1)*

- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for TBEP:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from effect-specific SV$_{HIGH}$ values for TBEP:* 3

Mean Comprehensive SV$_{LOW}$ for TBEP: 0.448 µg/L

- *Relative Confidence:* Very Low. Only three of the 13 effect categories are represented,

with two of the categories having only 1 SV point estimate each.

- *Representation in the Comprehensive SV$_{LOW}$ Dataset for TBEP (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo
  - Publication(s): Han et al. 2014, Springborn Bionomics, Inc. 1984
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (1):* equilibrium
    - *Developmental (2):* embryo heart rate, body weight, survival, and hatch rate, apoptosis in tail
    - *Mortality (1)*
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for TBEP:* ranged from 392 to 2937*(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for TBEP:* 3

Effect-Specific SV Values (ug/L) for TBEP

• Population-relevant SV_{HIGH}: The TBEP effect-specific Population-relevant SV_{HIGH} values in three effect categories range from 377 ug/L (Mortality) to 1,750 ug/L (Behavioral) (Table 4-1a).

• Population-relevant SV_{LOW}: Available data were sufficient to estimate values for three of the five population-relevant effect categories, with effect-specific population-relevant SV_{LOW} values ranging from 0.954 ug/L (Developmental) to 16.5 (Behavioral) (Table 4-1b).

• Comprehensive SV_{HIGH}: Three out of 13 effect categories had sufficient data to estimate effect-specific values, which range from 34.5 ug/L (Mortality) to 1,640 ug/L (Behavioral) (Table 4-1c).

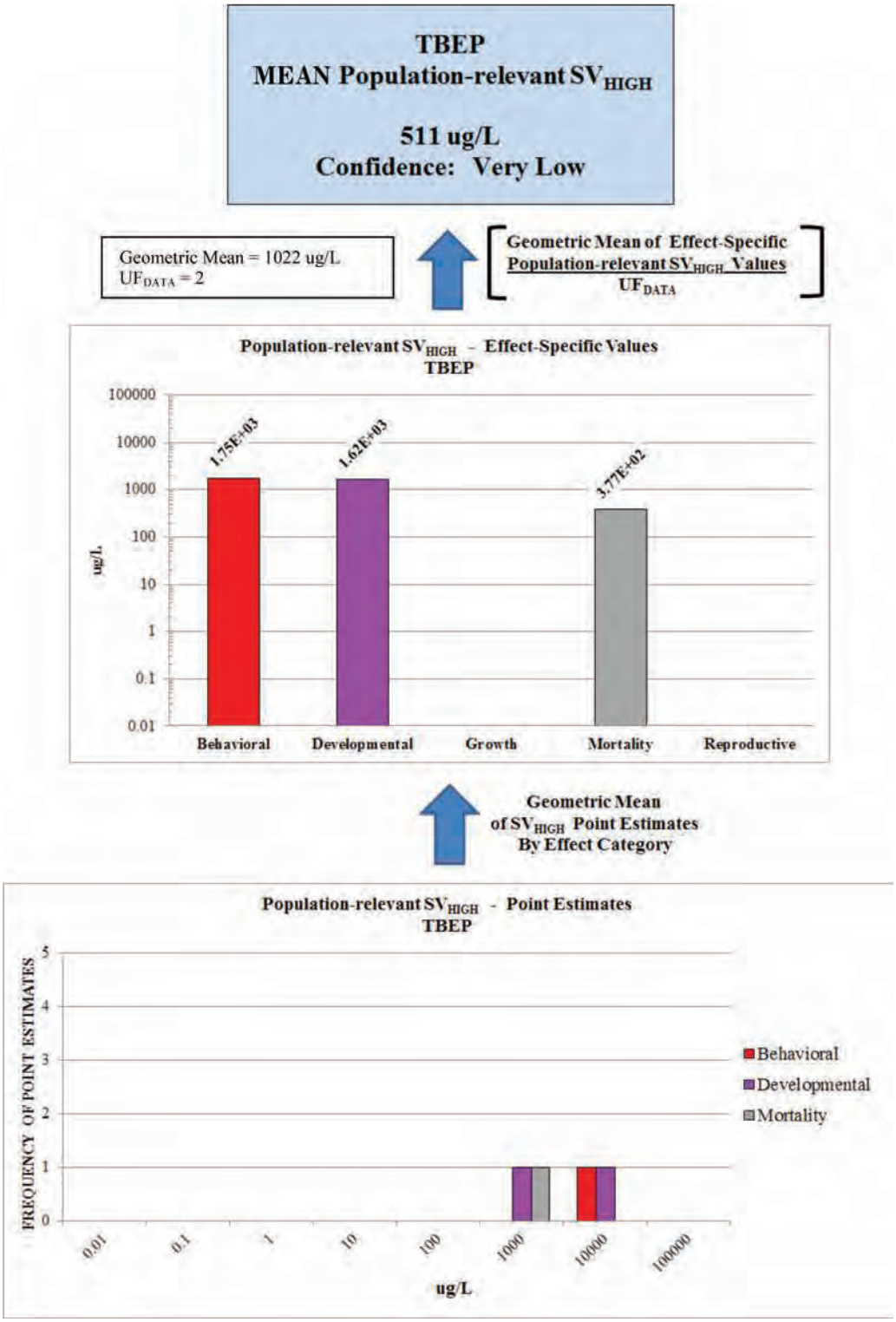
• Comprehensive SV_{LOW}: There were sufficient data to estimate values for three of the 13 effect categories, with values ranging from 0.383 ug/L (Developmental) to 6.64 ug/L (Behavioral) (Table 4-1d).

SV Point Estimates for TBEP

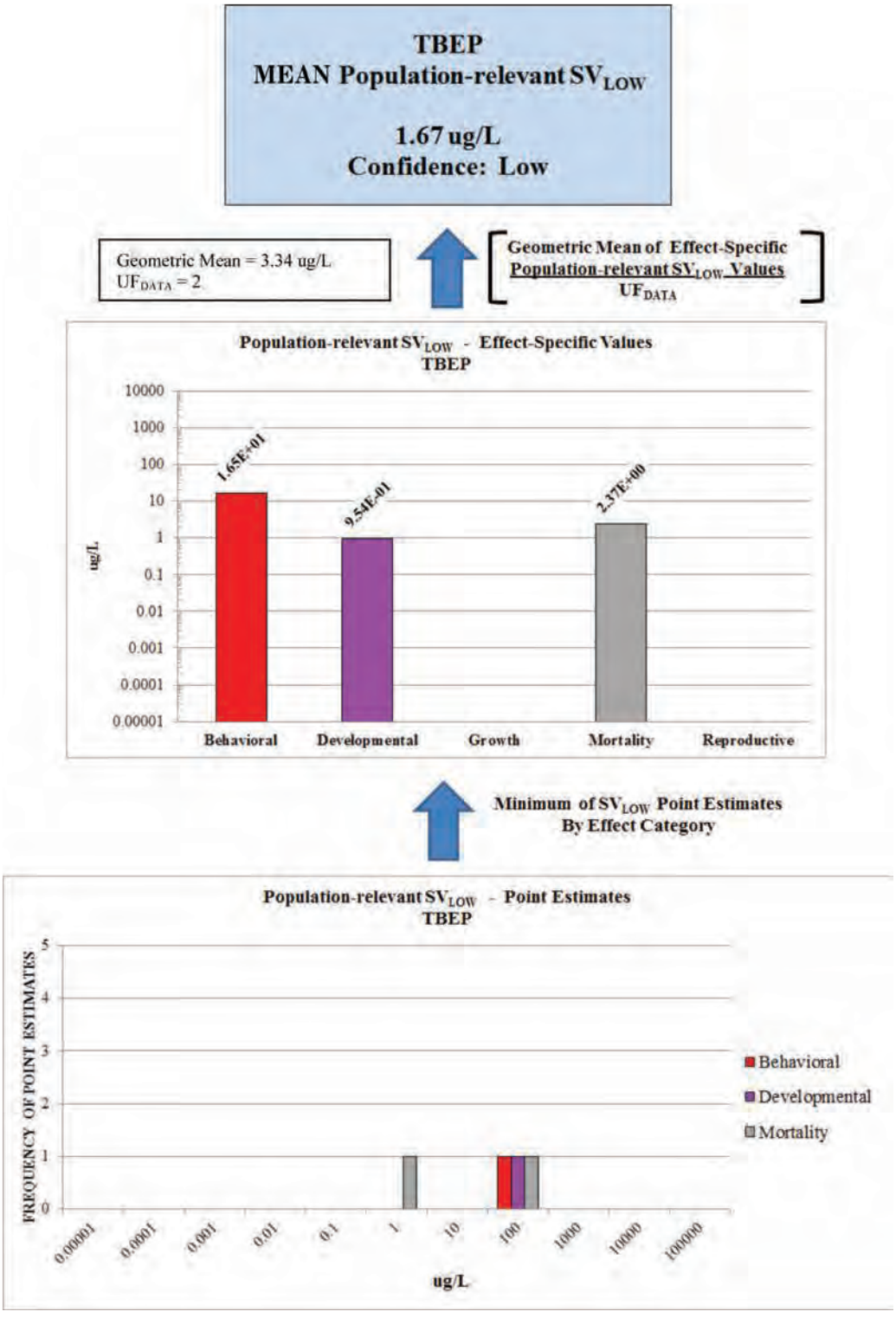
Effect Category	**TBEP Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category**			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	1751 (1)	16.5 (1)	1641 (1)	6.64 (1)
Developmental	323 – 8081 (2)	0.954 – 25.4 (2)	303 – 7575 (2)	0.383 – 10.2 (2)
Growth				
Mortality	377 (1)	2.37 (1)	354 (1)	0.953 (1)
Reproductive				
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				
Gross Pathology				
Histopathology				
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.12.3 SV Development: Graphics for TBEP

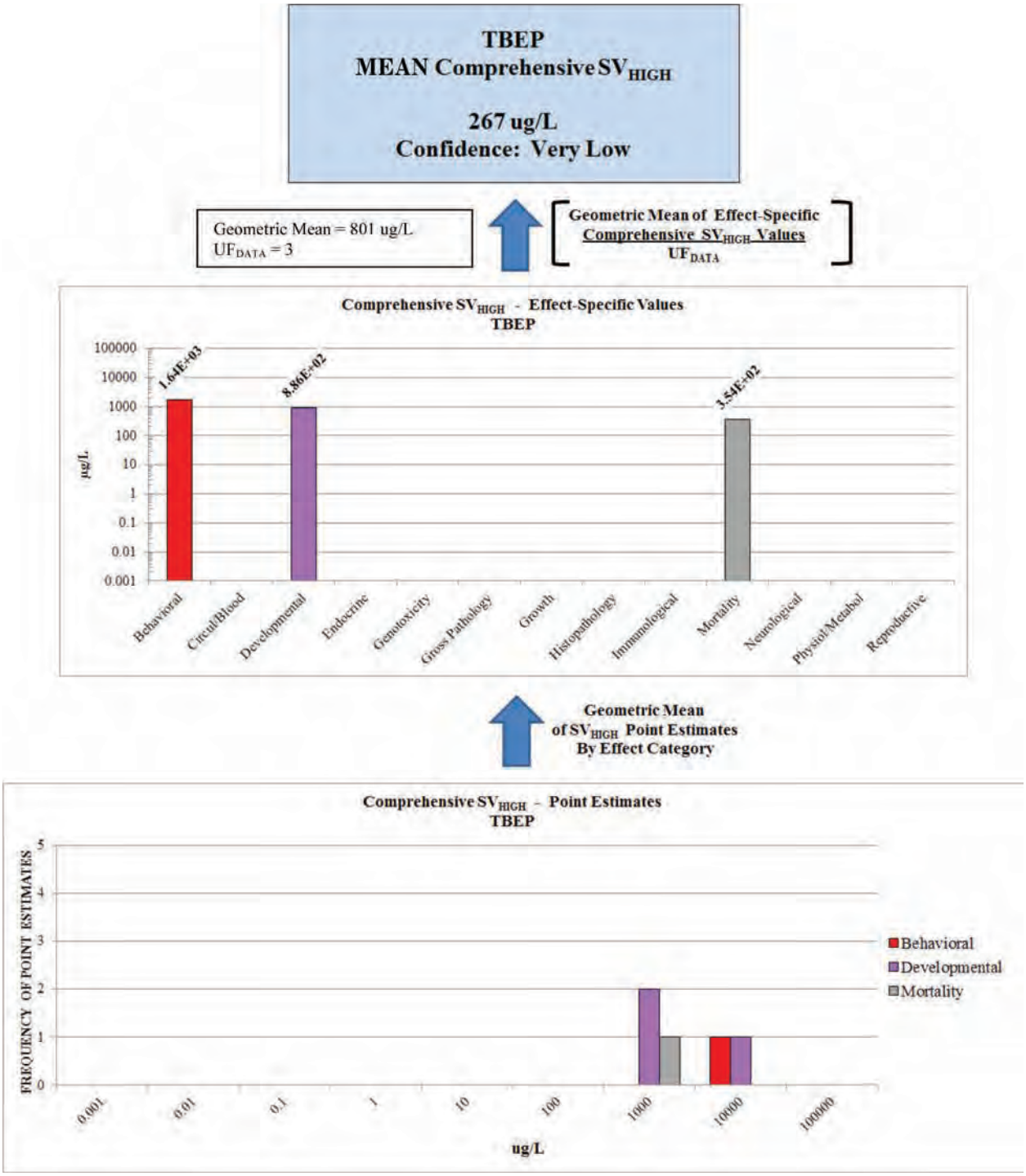
Population-relevant SV_{HIGH} Values for TBEP: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



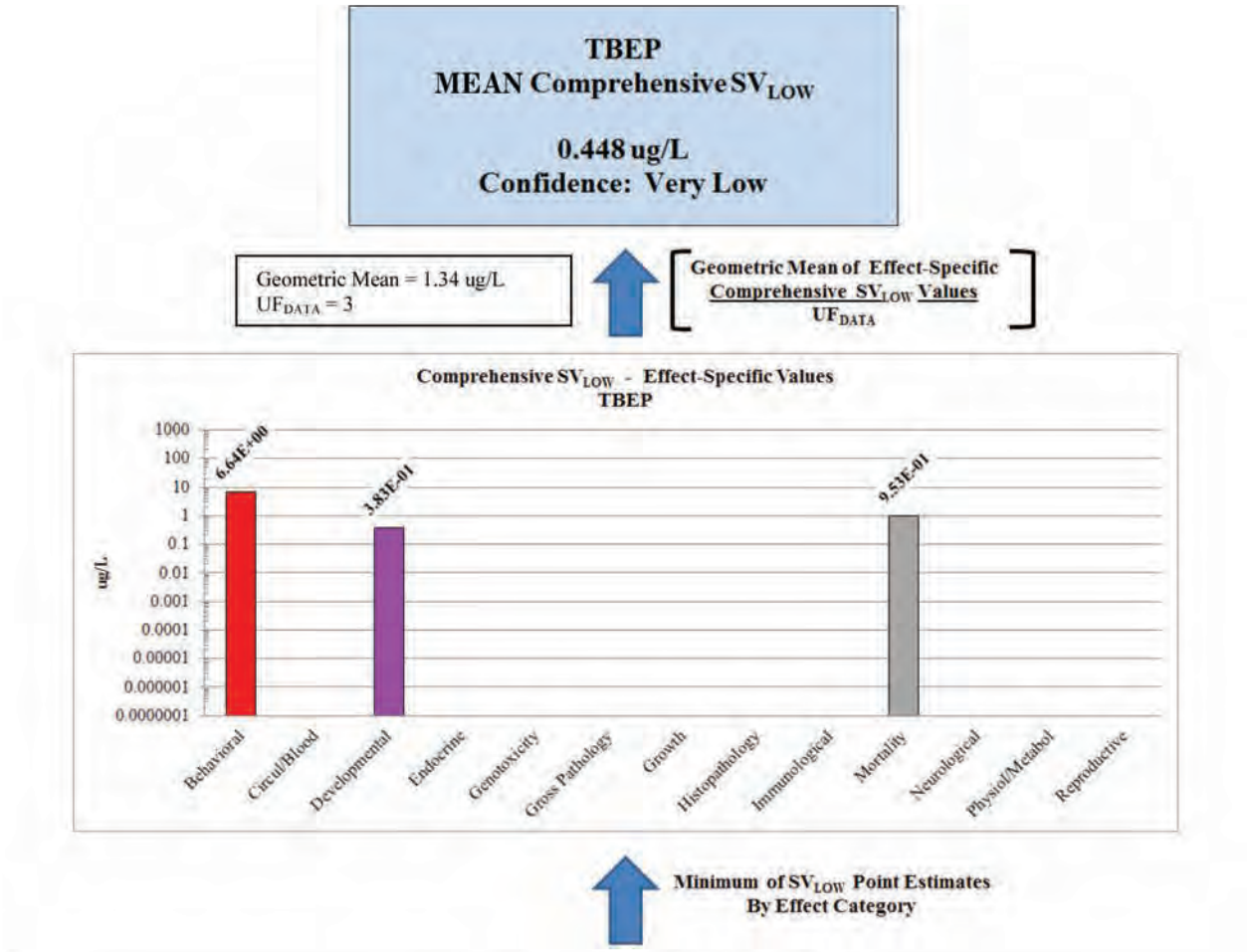
Population-relevant SV_{LOW} Values for TBEP: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

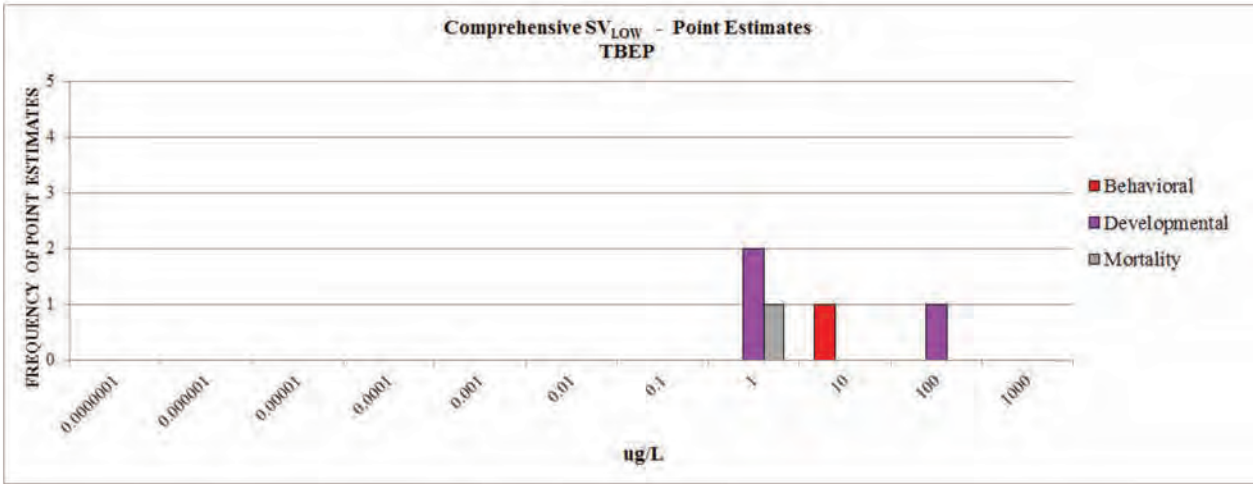


Comprehensive SV_{HIGH} Values for TBEP: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for TBEP: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.13 Triclosan

4.4.13.1 Chemical Summary

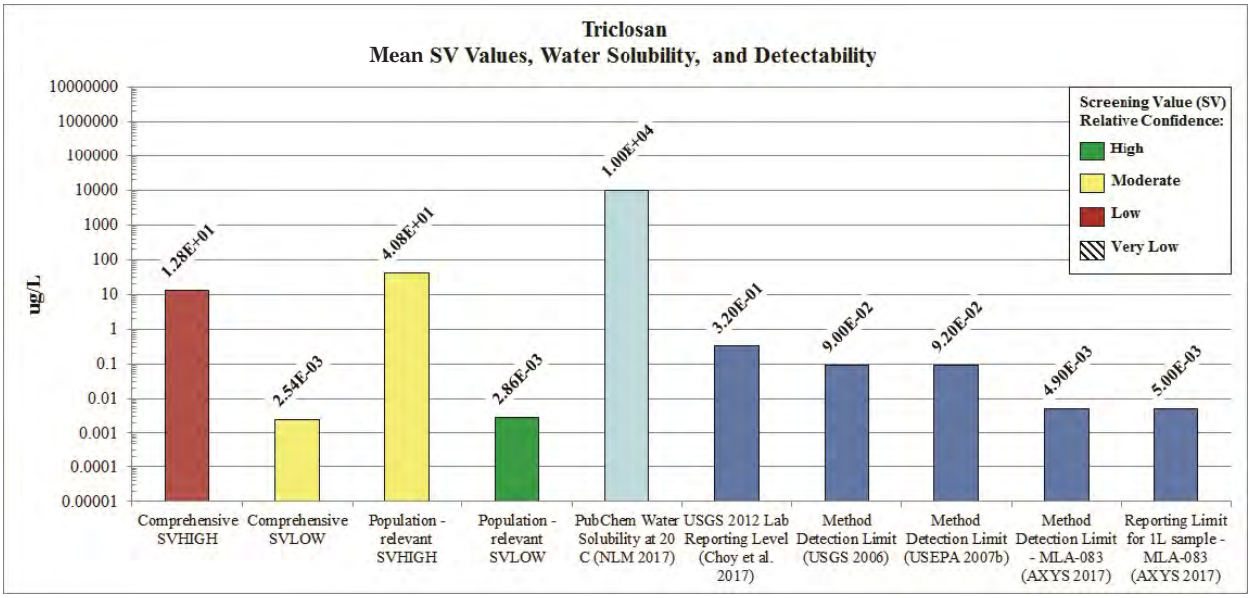
CEC Category: Personal Care Product
CEC Subcategories: Antimicrobial

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "Triclosan is a polychlorophenoxy phenol with antibacterial and antifungal activity. Triclosan is added to toothpastes to prevent gingivitis and has been added to many household products for its topical antibiotic activity."
- *CAS Number:* 3380-34-5
- *Water Solubility:* 10 mg/L at 20 deg C
- *logKow:* 4.76
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 0.32 ug/L*
- *Reporting Level - Techniques and Methods 5-B4 (USGS 2006): 1 ug/L*
- *MDL – Techniques and Methods 5-B4 (USGS 2006): 0.09 ug/L*
- *MDL – EPA Method 1694 (USEPA 2007b): 0.092 ug/L*
- *MDL – AXYS Method MLA-083 (AXYS 2017): 0.0049 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-083 (AXYS 2017): 0.005 ug/L*

4.4.13.2 Screening Value Summary

Mean SV Values (ug/L) for Triclosan



Mean Population-relevant SV$_{HIGH}$ for Triclosan: 40.8 μg/L

- *Relative Confidence:* Moderate. Although four of five population-relevant effect categories are represented, two of the categories have only 1 observation each.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Triclosan (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, mosquitofish, rainbow trout, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 7 studies published between 2000 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (4):* swimming speed, spontaneous swimming activity, feeding activity, swim-up, equilibrium, lock-jaw, erratic swimming, quiescence, opercular movement
    - *Developmental (4):* survival, spinal curvature, larval length and weight, percent hatch, time to hatch
    - *Mortality (1)*
    - *Reproductive (1):* sperm count, GSI
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Triclosan:* ranged from 2.5 to 7.4 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Triclosan:* 1

Mean Population-relevant SV$_{LOW}$ for Triclosan: 0.00286 μg/L

- *Relative Confidence.* High. All five of the population-relevant effect categories are represented, with between 2 and 6 observations in each category. The dataset includes effects information on five fish species and four life stages, compiled from eight separate publications.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Triclosan (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, mosquitofish, rainbow trout, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 8 studies published between 2000 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (6):* swimming speed, spontaneous swimming activity, feeding activity, swim-up, equilibrium, lock-jaw, erratic swimming, quiescence, opercular movement, nest defense, aggression index, larval escape performance metrics
    - *Developmental (5):* embryo and larval survival, spinal malformations, pericardial edema, larval length and weight, percent hatch, time to hatch, hatchability, secondary sex characteristics, otolith formation and pigmentation
    - *Growth (3):* body length and weight, condition factor
    - *Mortality (2)*
    - *Reproductive (3):* sperm count, GSI, gonad histopathology, secondary sex characteristics, fecundity, fertility, hatchability
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for Triclosan:* ranged from 78.6 to 786 *(see Attachment 4-2B for breakdown of the component UF values by SV pointestimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Triclosan:* 1

Mean Comprehensive SV$_{HIGH}$ for Triclosan: 12.8 μg/L

- *Relative Confidence:* Low. Only four of the 13 effect categories are represented, with two of the categories having only 1 observation each.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Triclosan (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, mosquitofish, rainbow trout, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 7 studies published between 2000 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (4):* swimming speed, spontaneous swimming activity, feeding activity, swim-up, equilibrium, lock-jaw, erratic swimming, quiescence, opercular movement
    - *Developmental (4):* embryo and larval survival, spinal malformations, pericardial edema, larval length and weight, percent hatch, time to hatch, hatchability, secondary sex characteristics, otolith formation and pigmentation
    - *Mortality (1)*
    - *Reproductive (1):* sperm count, GSI
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for Triclosan:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Triclosan:* 3

Mean Comprehensive SV$_{LOW}$ for Triclosan: 0.00254 μg/L

- *Relative Confidence:* Moderate. Although seven of the 13 effect categories are represented, three of those categories are represented by 2 or fewer observations.
- *Representation in the Comprehensive SV$_{LOW}$ Dataset for Triclosan (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, Japanese medaka, mosquitofish, rainbow trout, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): 8 studies published between 2000 and 2013
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (6):* swimming speed, spontaneous swimming activity, feeding activity, swim-up, equilibrium, lock-jaw, erratic swimming, quiescence, opercular movement, nest defense, aggression index, larval escape performance metrics
    - *Developmental (5):* embryo and larval survival, spinal malformations, pericardial edema, larval length and weight, percent hatch, time to hatch, hatchability, secondary sex characteristics, otolith formation and pigmentation
    - *Genotoxicity (1):* micronucleus test
    - *Growth (3):* body length and weight, condition factor
    - *Histopathology (1):* liver
    - *Mortality (2)*
    - *Reproductive (3):* sperm count, GSI, gonad histopathology, secondary sex characteristics, fecundity, fertility, hatchability
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Triclosan:* ranged from 196 to 1958 (see Attachment 4-2D for breakdown of the component UF values by SV point estimate)
- *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Triclosan:* 1

Effect-Specific SV Values (ug/L) for Triclosan

• Population-relevant SV_{HIGH}: The triclosan effect-specific population-relevant SV_{HIGH} values in four effect categories range from 22.8 ug/L (Behavioral) to 73.8 ug/L (Developmental) (Table 4-1a).

• Population-relevant SV_{LOW} : Available data were sufficient to estimate values for all five population-relevant effect categories, with all five effect-specific population-relevant SV_{LOW} values identified as 0.00286 ug/L (Table 4-1b).

• Comprehensive SV_{HIGH} : Four out of 13 effect categories had sufficient data to estimate effect-specific values, which range from 21.4 ug/L (Behavioral) to 69.2 ug/L (Developmental) (Table 4-1c).

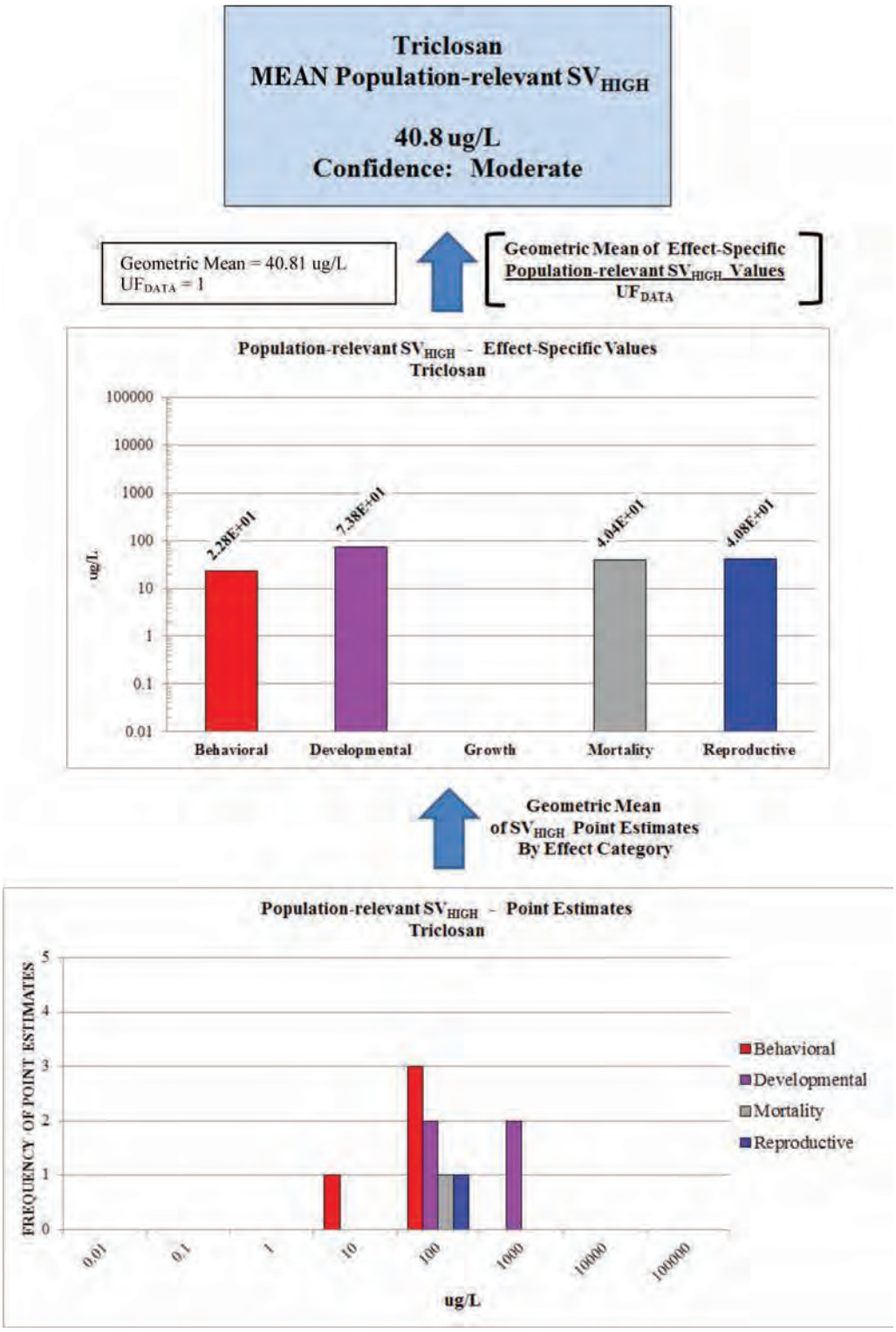
• Comprehensive SV_{LOW} : There were sufficient data to estimate values for seven of the 13 effect categories. However, six of the categories share the same SV_{LOW} value, 0.00115 ug/L, which is derived from effects data reported in a single study (Schultz et al. 2012). Values range from 0.00115 ug/L (6 categories) to 0.298 ug/L (Genotoxicity) (Table 4-1d).

SV Point Estimates for Triclosan

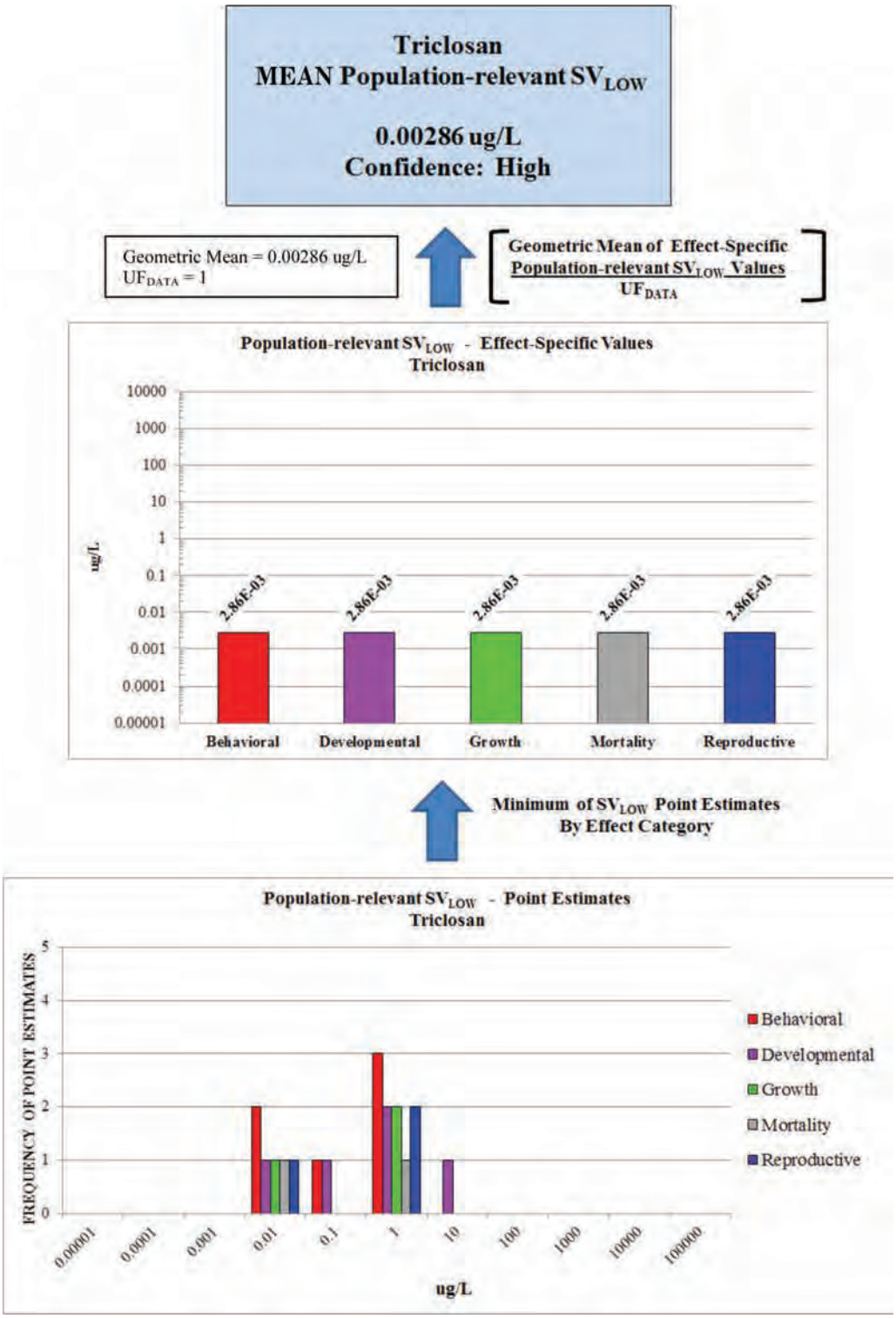
Effect Category	Triclosan Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	4.04 – 67.3 (4)	0.00286 – 0.848 (6)	3.79 – 63.1 (4)	0.00115 – 0.34 (6)
Developmental	28.8 – 202 (4)	0.00286 – 1.91 (5)	27.0 – 189 (4)	0.00115 – 0.77 (5)
Growth		0.00286 – 0.871 (3)		0.00115 – 0.35 (3)
Mortality	40.4 (1)	0.00286 – 0.424 (2)	37.9 (1)	0.00115 – 0.17 (2)
Reproductive	40.8 (1)	0.00286 – 0.871 (3)	38.3 (1)	0.00115 – 0.35 (3)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine				
Genotoxicity				0.3 (1)
Gross Pathology				
Histopathology				0.00115 (1)
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.13.3 SV Development: Graphics for Triclosan

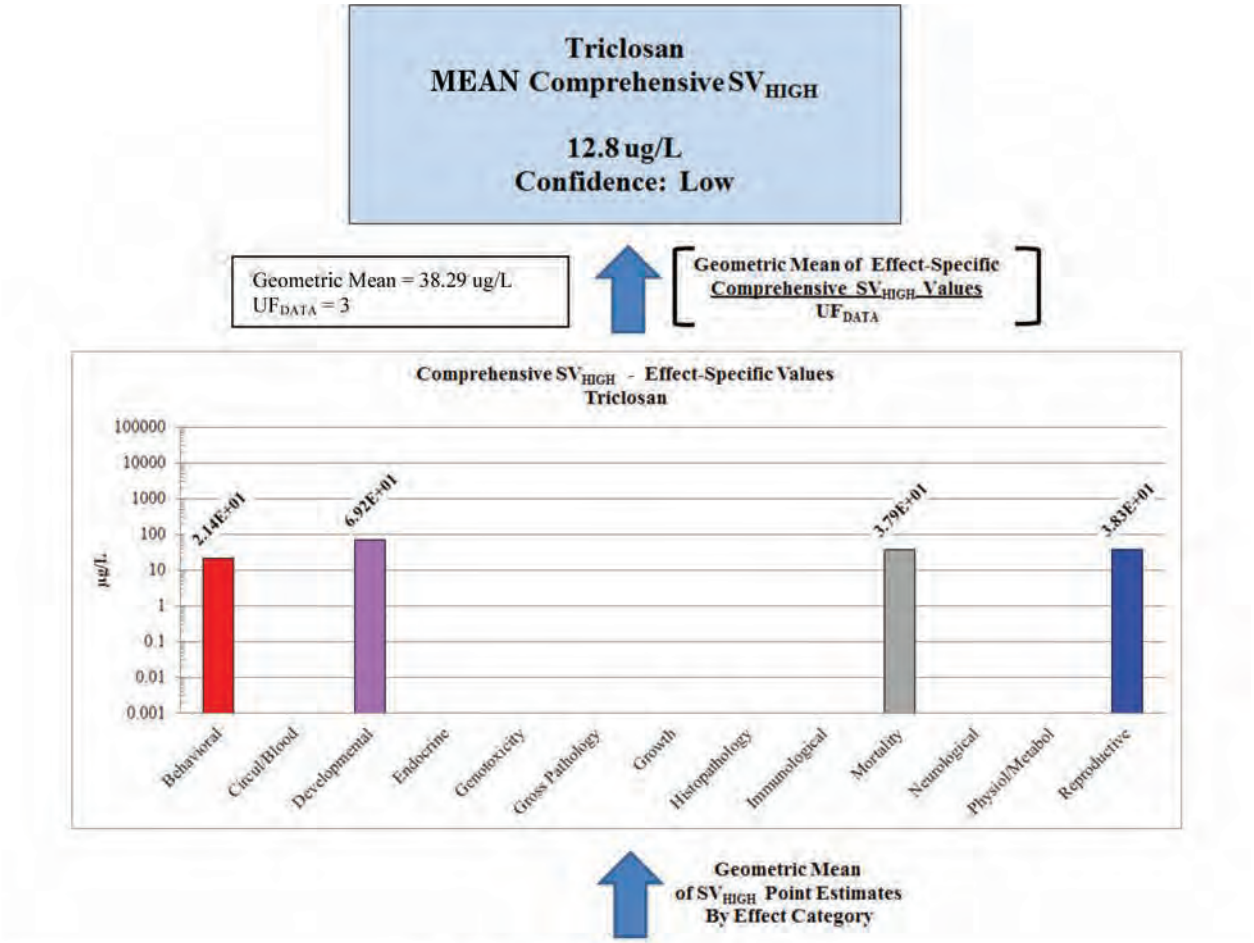
Population-relevant SV_{HIGH} Values for Triclosan: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

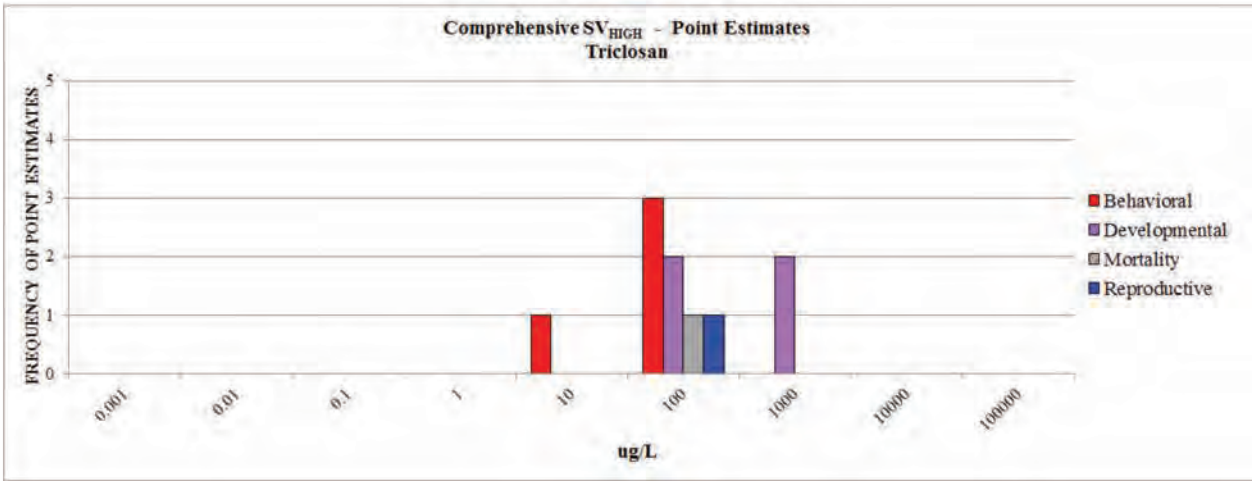


Population-relevant SV_{LOW} Values for Triclosan: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

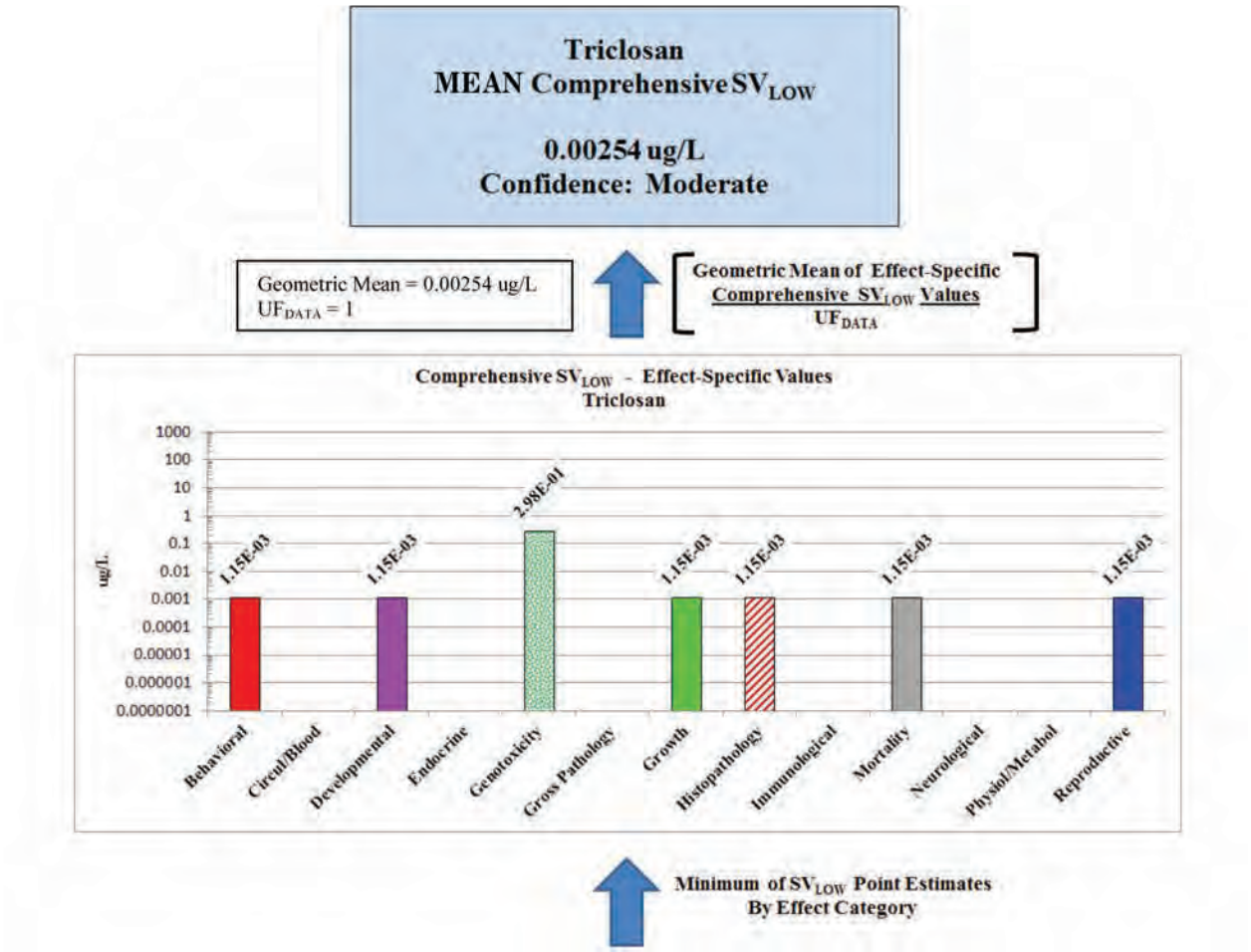


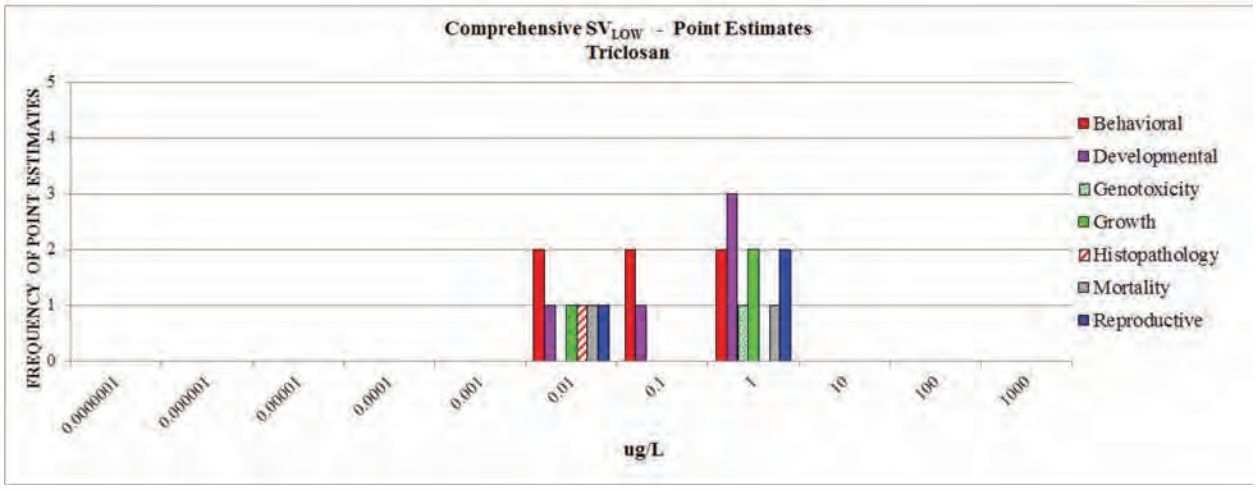
Comprehensive SV_{HIGH} Values for Triclosan: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





Comprehensive SV_{LOW} Values for Triclosan: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





4.4.14 Venlafaxine

4.4.14.1 Chemical Summary

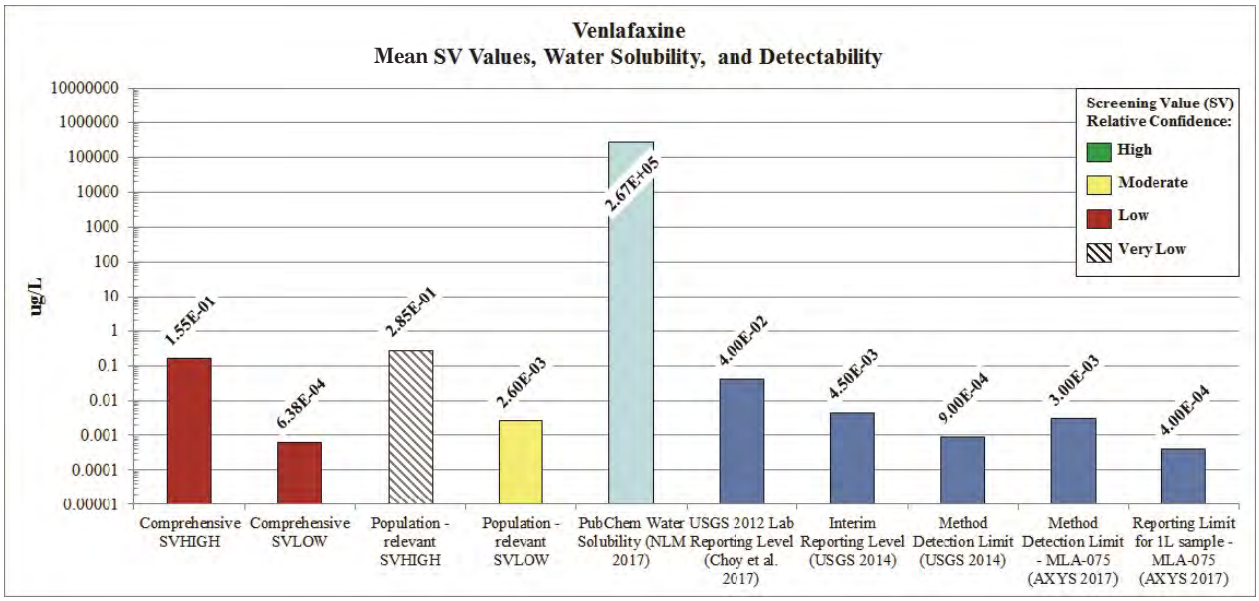
CEC Category: Pharmaceutical
CEC Subcategories: Antidepressant

The following chemical information was obtained from the PubChem database (NLM 2016) , unless otherwise indicated:

- *Usage:* "Venlafaxine is a serotonin and norepinephrine reuptake inhibitor widely used as an antidepressant."
- *CAS Number:* 93413-69-5
- *Water Solubility:* 267 mg/L (as the hydrochloride salt)
- *logKow:* 3.20
- *2010-2012 USGS Laboratory Reporting Level (Choy et al. 2017): 0.04 ug/L*
- *Interim Reporting Level - Techniques and Methods 5-B10 (USGS 2014): 0.0045 ug/L*
- *MDL – Techniques and Methods 5-B10 (USGS 2014): 0.0009 ug/L*
- *MDL – AXYS Method MLA-075 (AXYS 2017): 0.003 ug/L*
- *Reporting Limit for 1L sample – AXYS Method MLA-075 (AXYS 2017): 0.0004 ug/L*

4.4.14.2 Screening Value Summary

Mean SV Values (ug/L) for Venlafaxine



Mean Population-relevant SV$_{HIGH}$ for Venlafaxine: 0.285 µg/L

- *Relative Confidence:* Very Low. Three of five population-relevant effect categories are represented, but two of the categories have only 1 observation each.
- *Representation in the Population-relevant SV$_{HIGH}$ Dataset for Venlafaxine (see Attachment 4-2A: Population-relevant SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Galus et al. 2013a, Painter et al. 2009, Schultz et al. 2011, Thomas et al. 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although LOAECs for population-relevant endpoints were the basis for deriving SV$_{HIGH}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (3):* larval total escape response, startle response
    - *Mortality (1)*
    - *Reproductive (1):* embryo production, spermatogenesis, testis morphology, testis apoptosis, gonad histopathology, reproductive hormone levels
- *Cumulative Uncertainty Factors applied to LOAEC values to obtain Population-relevant SV$_{HIGH}$ point estimates for Venlafaxine:* ranged from 2.5 to 5 *(see Attachment 4-2A for breakdown of component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Venlafaxine:* 2

Mean Population-relevant SV$_{LOW}$ for Venlafaxine: 0.0026 µg/L

- *Relative Confidence.* Moderate. Although all five of the population-relevant effect categories are represented, two of the categories have only 1 observation each.
- *Representation in the Population-relevant SV$_{LOW}$ Dataset for Venlafaxine (see Attachment 4-2B: Population-relevant SV$_{LOW}$ Point Estimates)*
  - Species: fathead minnow, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Galus et al. 2013, Painter et al. 2009, Schultz et al. 2011, Thomas et al. 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study. Although NOAECs and unbounded LOAECs for population-relevant endpoints were the basis for deriving SV$_{LOW}$ values, all evaluated endpoints are listed here. Population-relevance of effect endpoints is discussed in Section 2.5 and Figure 2.2, and listed in Attachment 2-1.
    - *Behavioral (3):* larval total escape response, startle response, response latency
    - *Developmental (3):* body length, embryo survival, total abnormalities
    - *Growth (1):* condition factor
    - *Mortality (1)*
    - *Reproductive (2):* embryo production, spermatogenesis, testis morphology, testis apoptosis, gonad histopathology, reproductive hormone levels, male secondary sex characteristic scores, GSI
- *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Population-relevant SV$_{LOW}$ point estimates for Venlafaxine:* ranged from 78.6 to 786 *(see Attachment 4-2B for breakdown of the component UF values by SV point estimate)*
- *Database Adequacy UF applied to obtain the Mean Population-relevant SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Venlafaxine:* 1

Mean Comprehensive SV$_{HIGH}$ for Venlafaxine: 0.155 µg/L

- *Relative Confidence:* Low. Six of 13 effect categories are represented, but three of those have only 1 observation each.
- *Representation in the Comprehensive SV$_{HIGH}$ Dataset for Venlafaxine (see Attachment 4-2C: Comprehensive SV$_{HIGH}$ Point Estimates)*
  - Species: fathead minnow, rainbow trout, zebrafish
  - Life Stage(s): embryo, larva, juvenile, adult
  - Publication(s): Best et al. 2014, Galus et al. 2013a, Painter et al. 2009, Schultz et al. 2011, Thomas et al. 2012
  - Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
    - *Behavioral (3):* larval total

escape response, startle response, response latency
- *Developmental (1)*
- *Endocrine/Hormone (1):* plasma cortisol in multiple stress test
- *Histopathology (1):* kidney, liver
- *Mortality (1)*
- *Reproductive (2):* embryo production, spermatogenesis, testis morphology, testis apoptosis, gonad histopathology, reproductive hormone levels, male secondary sex characteristic scores, GSI

o *Cumulative Uncertainty Factors applied to LOAEC values to obtain Comprehensive SV$_{HIGH}$ point estimates for Venlafaxine:* ranged from 2.6 to 7.9 *(see Attachment 4-2C for breakdown of component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{HIGH}$ value from Effect-Specific SV$_{HIGH}$ values for Venlafaxine:* 1

Mean Comprehensive SV$_{LOW}$ for Venlafaxine: 0.000638 µg/L

o *Relative Confidence:* Low. Seven of 13 effect categories are represented, but five of those have only 2 or fewer observations.

o *Representation in the Comprehensive SV$_{LOW}$ Dataset for Venlafaxine (see Attachment 4-2D: Comprehensive SV$_{LOW}$ Point Estimates)*

- Species: fathead minnow, rainbow trout, zebrafish
- Life Stage(s): embryo, larva, juvenile, adult
- Publication(s): Best et al. 2014, Galus et al. 2013, Painter et al. 2009, Schultz et al. 2011, Thomas et al. 2012
- Effect Categories (Number of SV Point Estimates), and Endpoints Evaluated in at least one Study
  - *Behavioral (3):* larval total escape response, startle response, response latency
  - *Developmental (3)*
  - *Endocrine/Hormone (1):* plasma cortisol in multiple stress test
  - *Growth (1):* condition factor
  - *Histopathology (2):* kidney, liver, brain
  - *Mortality (1)*
  - *Reproductive (2):* embryo production, spermatogenesis, testis morphology, testis apoptosis, gonad histopathology, reproductive hormone levels, male secondary sex characteristic scores, GSI

o *Cumulative Uncertainty Factors applied to NOAEC (bounded and unbounded) and Unbounded LOAEC values to obtain Comprehensive SV$_{LOW}$ point estimates for Venlafaxine:* ranged from 196 to 2937 *(see Attachment 4-2D for breakdown of the component UF values by SV point estimate)*

o *Database Adequacy UF applied to obtain the Mean Comprehensive SV$_{LOW}$ value from Effect-Specific SV$_{LOW}$ values for Venlafaxine:* 1

Effect-Specific SV Values (ug/L) for Venlafaxine

• Population-relevant SV_{HIGH}: The venlafaxine effect-specific population-relevant SV_{HIGH} values in three effect categories range from 0.0616 ug/L (Mortality) to 4.04 ug/L (Reproductive) (Table 4-1a).

• Population-relevant SV_{LOW} : Available data were sufficient to estimate values for all five population-relevant effect categories, with effect-specific population-relevant SV_{LOW} values ranging from 0.00065 ug/L (Mortality and Reproductive) to 0.0318 (Developmental) (Table 4-1b).

• Comprehensive SV_{HIGH} : Five out of 13 effect categories had sufficient data to estimate effect-specific values, which range from 0.0253 ug/L (Endocrine) to 0.698 ug/L (Behavioral) (Table 4-1c).

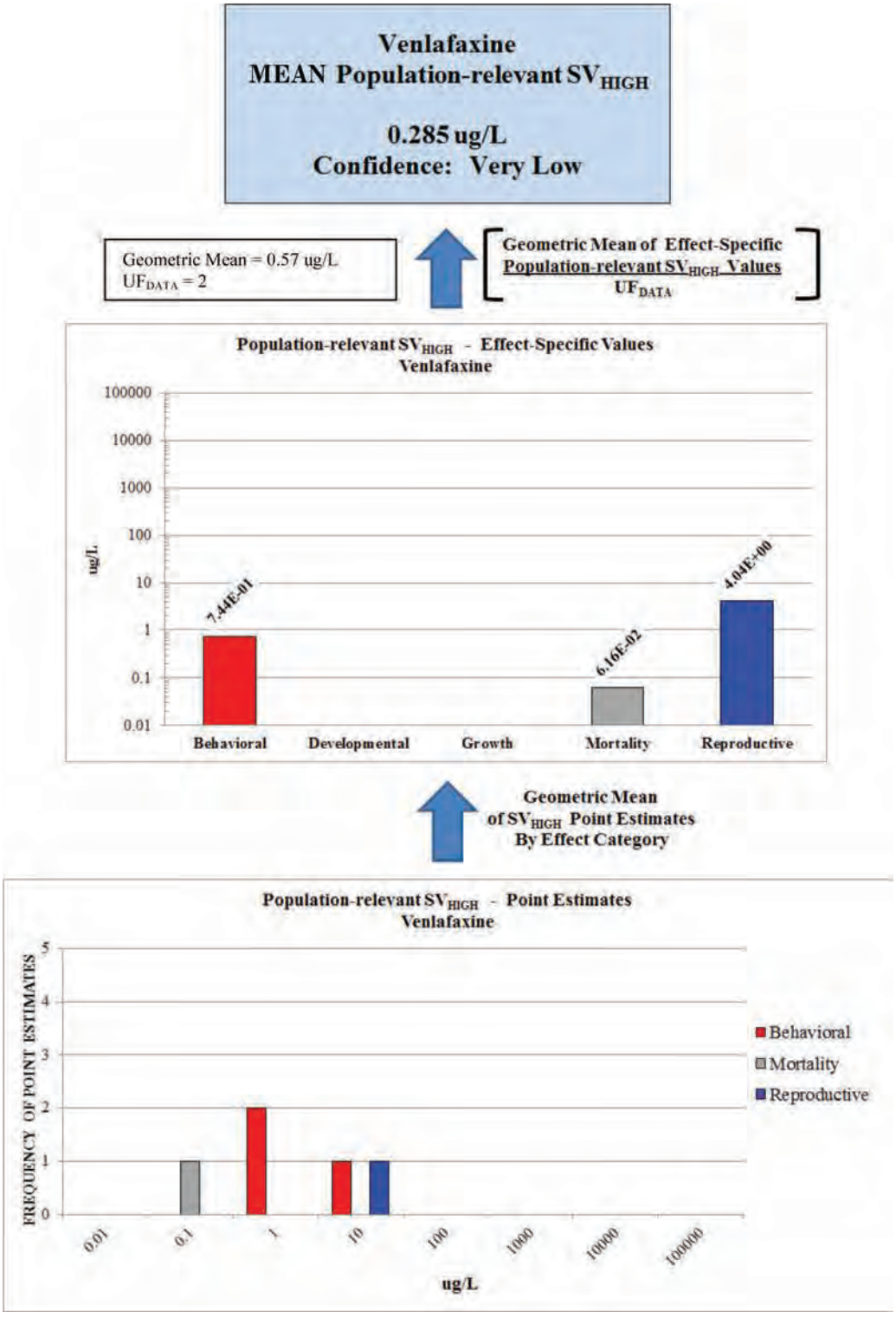
• Comprehensive SV_{LOW} : There were sufficient data to estimate values for seven of the 13 effect categories, with values ranging from 0.0000681 ug/L (Endocrine) to 0.0128 ug/L (Developmental) (Table 4-1d).

SV Point Estimates for Venlafaxine

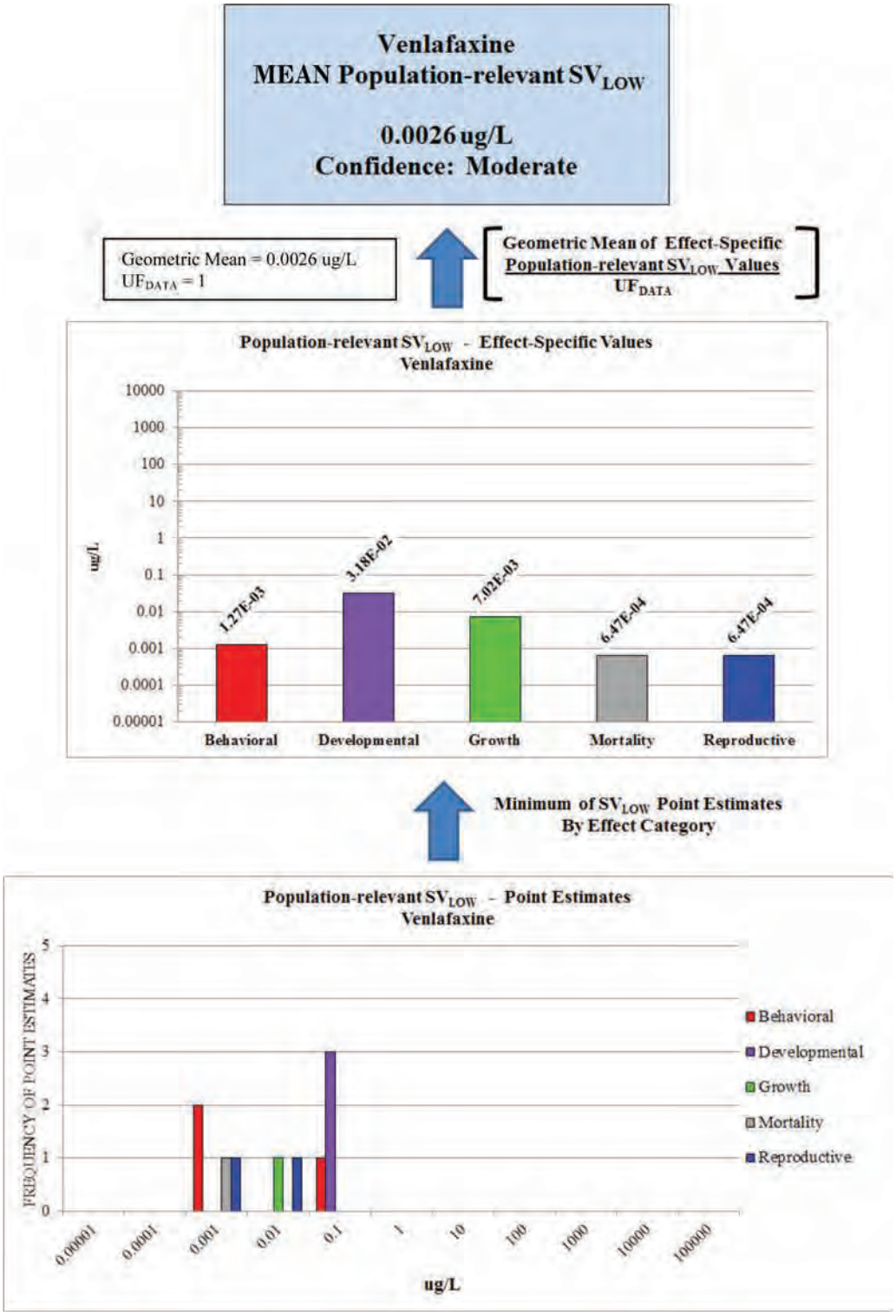
Effect Category	Venlafaxine Range (N) of SV Point Estimate Values (ug/L) by Type of SV and Effect Category			
	Population-relevant SV_{HIGH}	***Population-relevant SV_{LOW}***	***Comprehensive SV_{HIGH}***	***Comprehensive SV_{LOW}***
Effect Categories used for both Population-relevant and Comprehensive type SVs				
Behavioral	0.202 – 10.1 (3)	0.00127 – 0.0636 (3)	0.189 – 9.47 (3)	0.000511 – 0.0255 (3)
Developmental		0.0318 – 0.0553 (3)	0.0253 (1)	0.0128 – 0.0222 (3)
Growth		0.00702 (1)		0.00282 (1)
Mortality	0.062 (1)	0.000647 (1)	0.0578 (1)	0.00026 (1)
Reproductive	4.04 (1)	0.000647 – 0.00318 (2)	0.0578 – 3.79 (2)	0.00026 – 0.00128 (2)
Effect Categories used for Comprehensive type SVs, only				
Circulatory/ Blood Constituents				
Endocrine			0.0253 (1)	0.0000681 (1)
Genotoxicity				
Gross Pathology				
Histopathology			0.189 (1)	0.000511 – 0.00282 (2)
Immunological				
Neurological				
Physiology/ Metabolism				

4.4.14.3 SV Development: Graphics for Venlafaxine

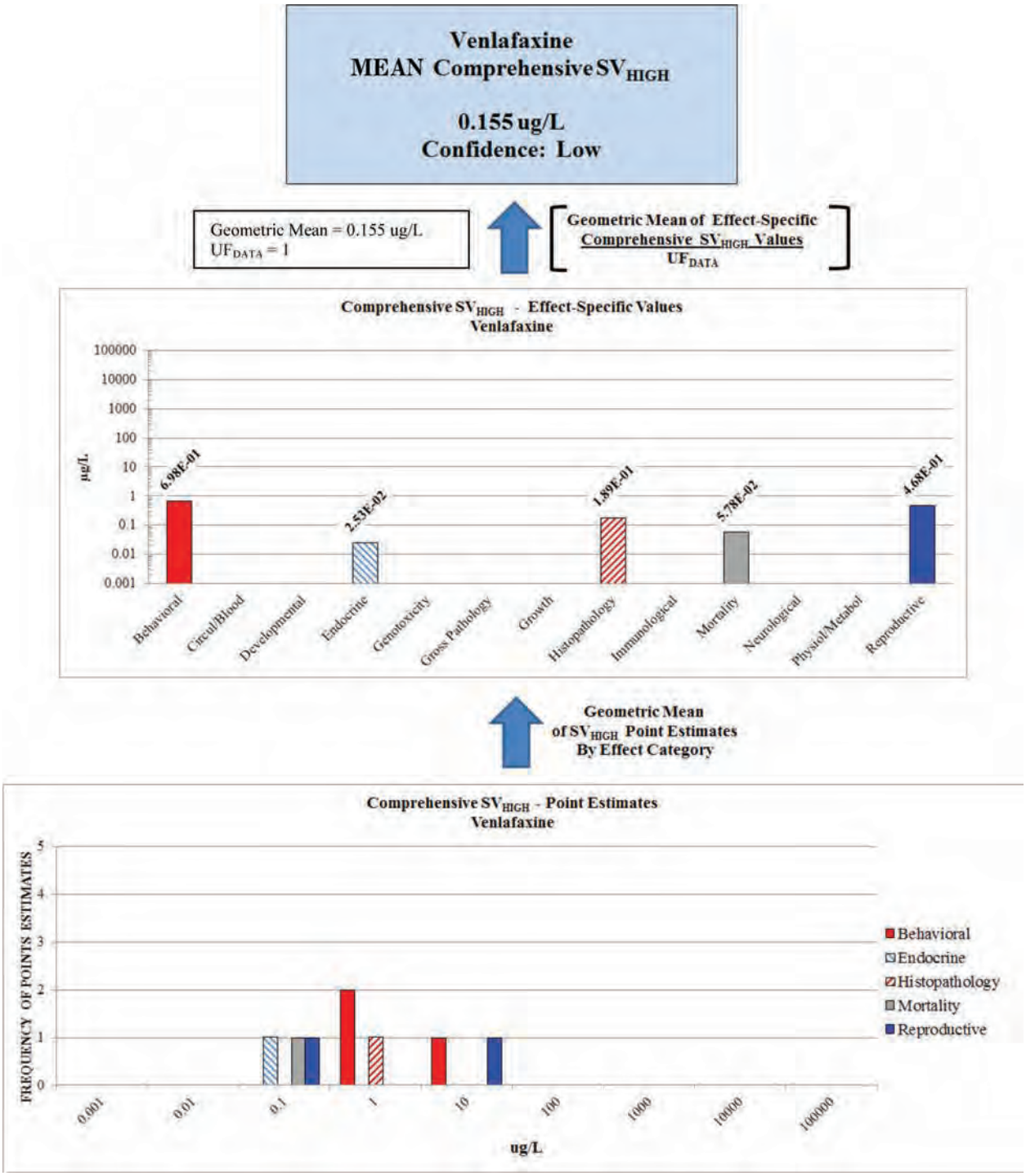
Population-relevant SV_{HIGH} Values for Venlafaxine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



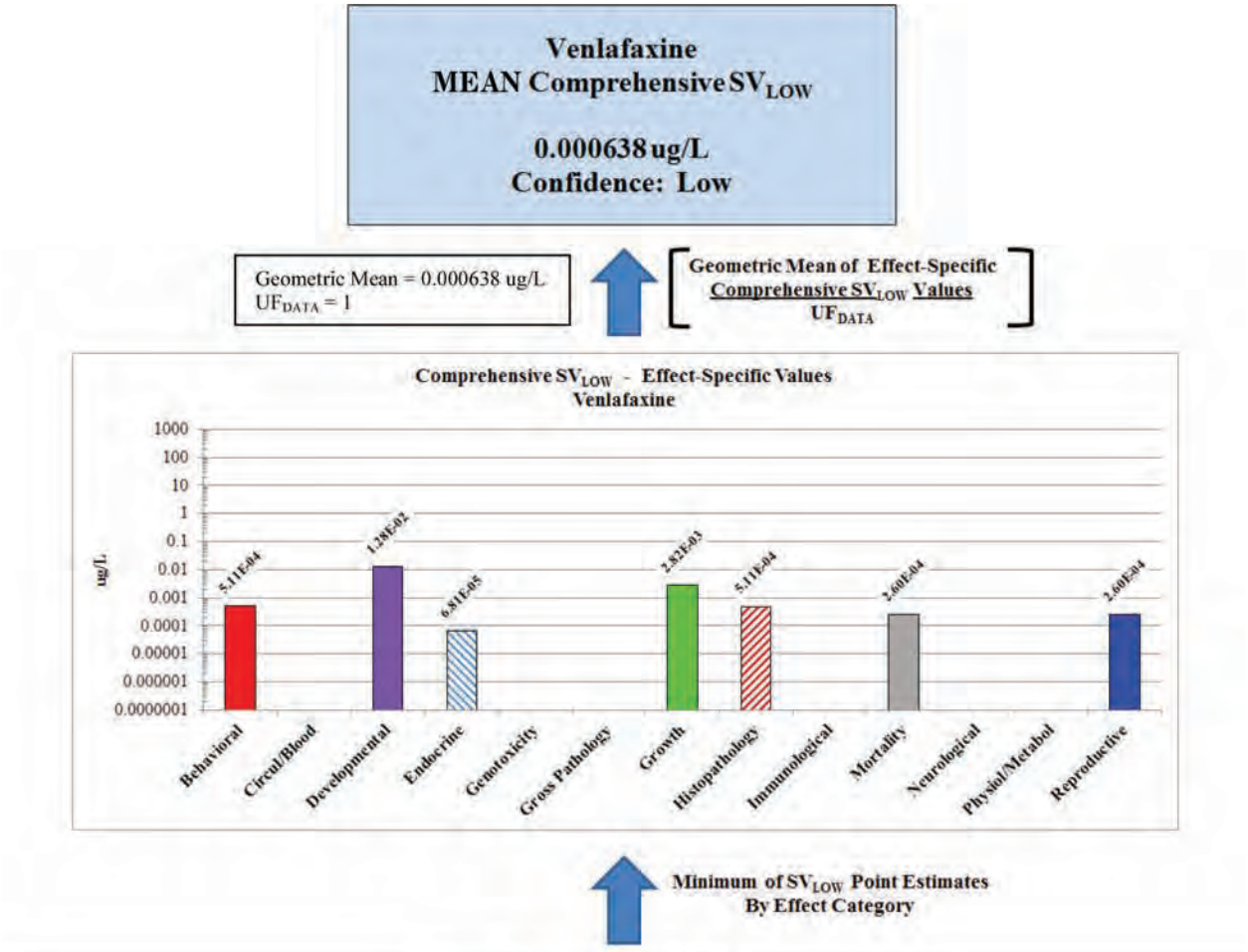
Population-relevant SV_{LOW} Values for Venlafaxine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.

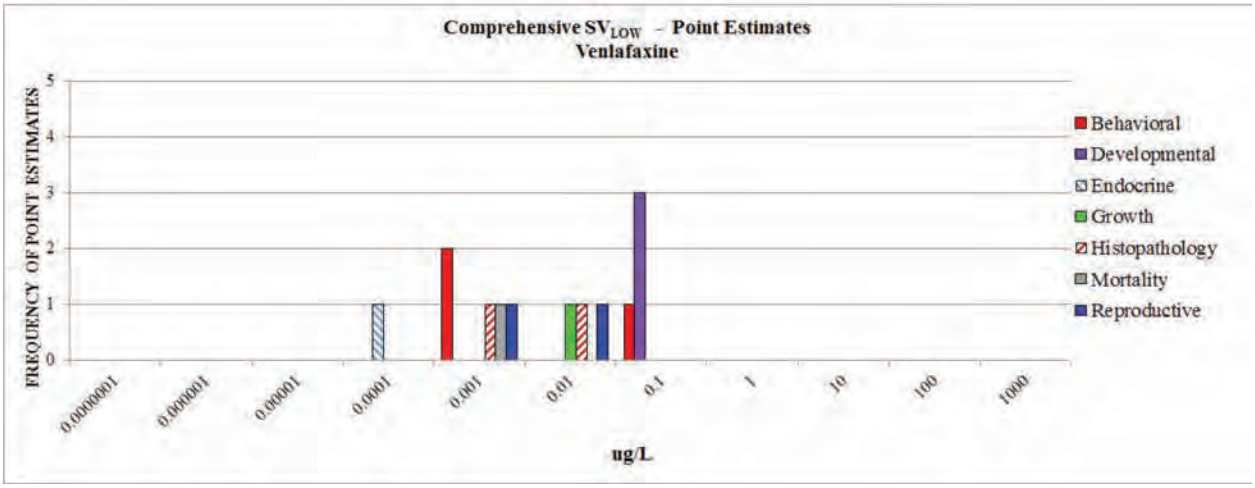


Comprehensive SV_{HIGH} Values for Venlafaxine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.



Comprehensive SV_{LOW} Values for Venlafaxine: Relationships among the Mean Value, Effect-Specific Values, and Point Estimates. In the Point Estimate histogram, the X-axis values are upper bounds of frequency distribution bin intervals.





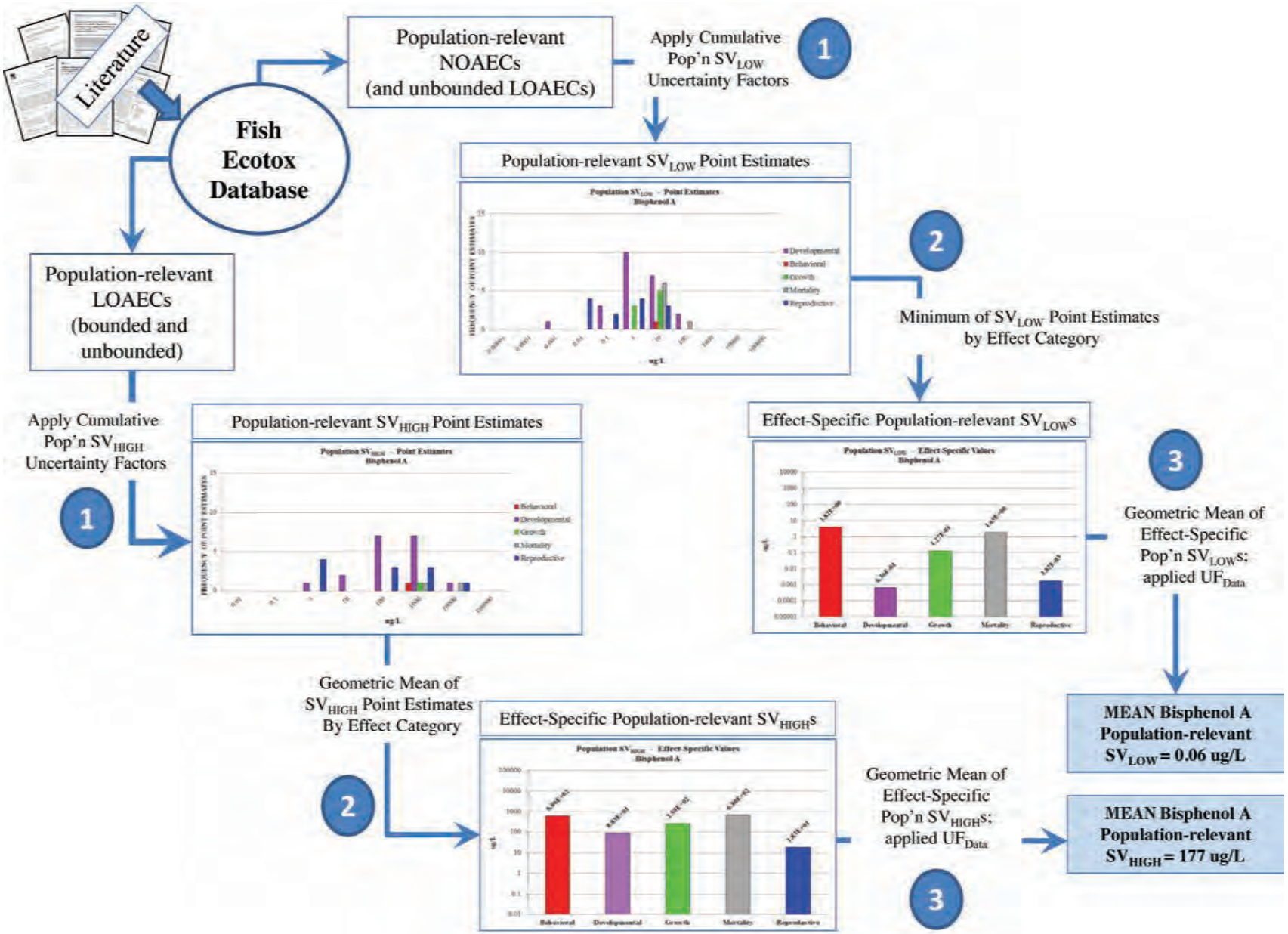


Figure 4-1. This three-step process of increasing aggregation of literature ecotoxicity information yields three types of SV$_{HIGH}$ and SV$_{LOW}$ values for each CEC: (1) Distributions of SV point estimates, (2) Effect-specific SVs, and (3) Mean CEC-specific SVs. Illustrated are the derivation steps for population-relevant SVs for Bisphenol A. A parallel process was used for deriving comprehensive SVs.

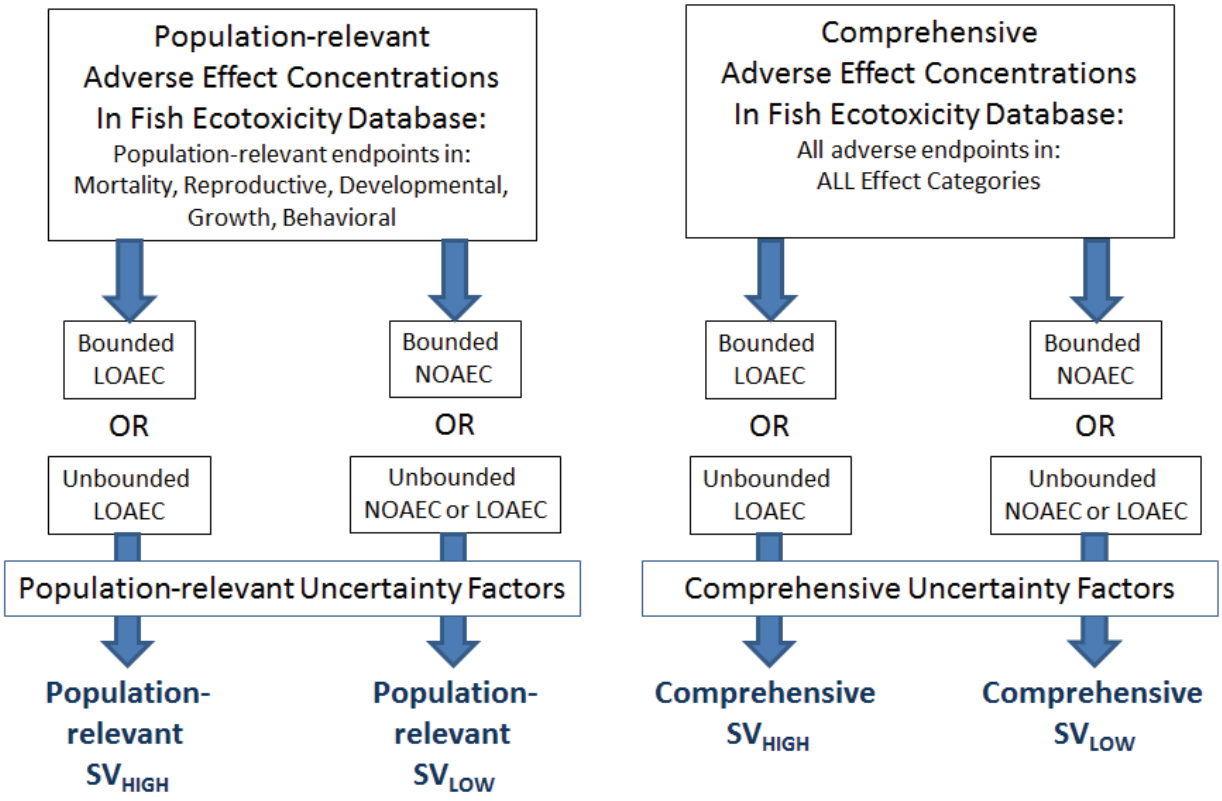


Figure 4-2. Derivation of four types of SV Point Estimates from adverse effect concentrations reported in the literature and compiled in the CEC Fish Ecotoxicity Database

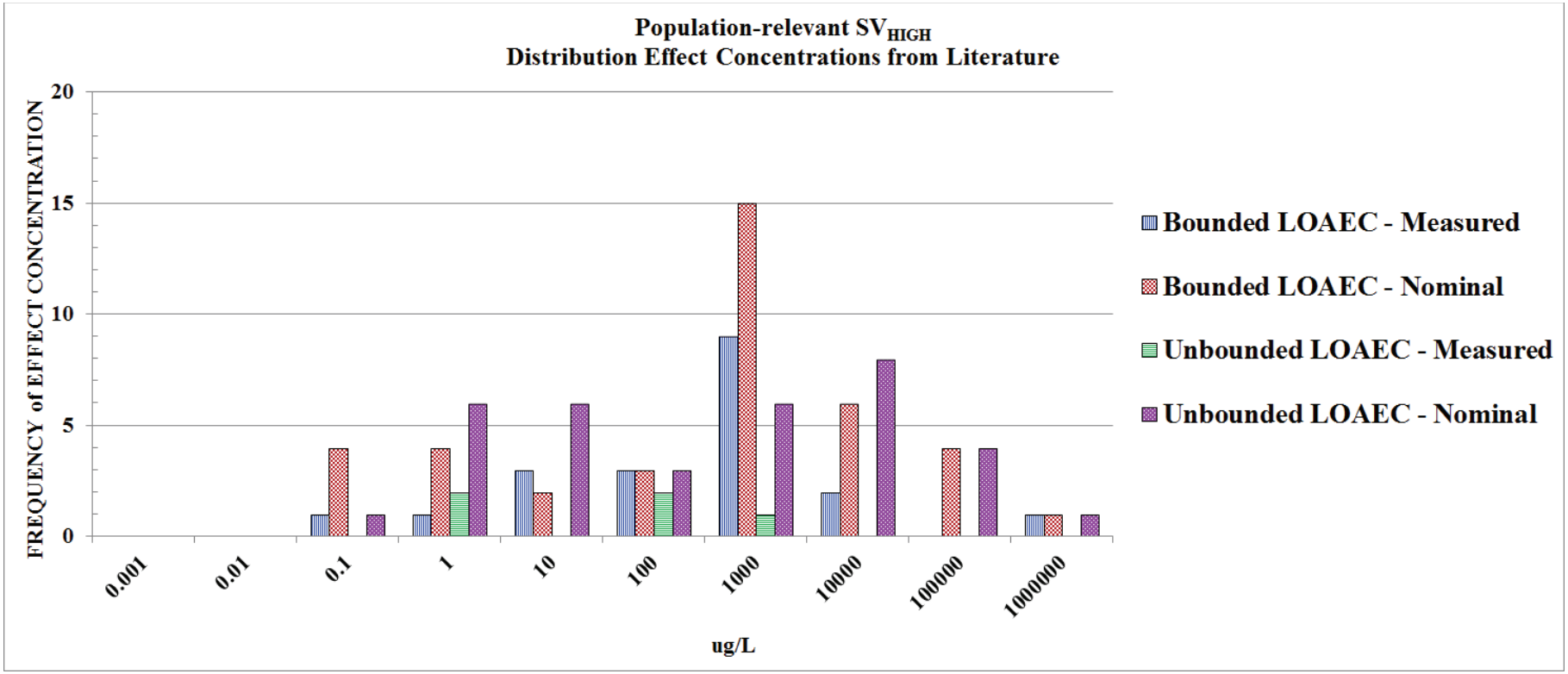


Figure 4-3. Distribution of unadjusted effect concentrations (ug/L) used to derive the population-relevant SVHIGH point estimates (N = 99) for the 14 CECs included in this document. X-axis values are upper bounds of frequency distribution bin intervals.

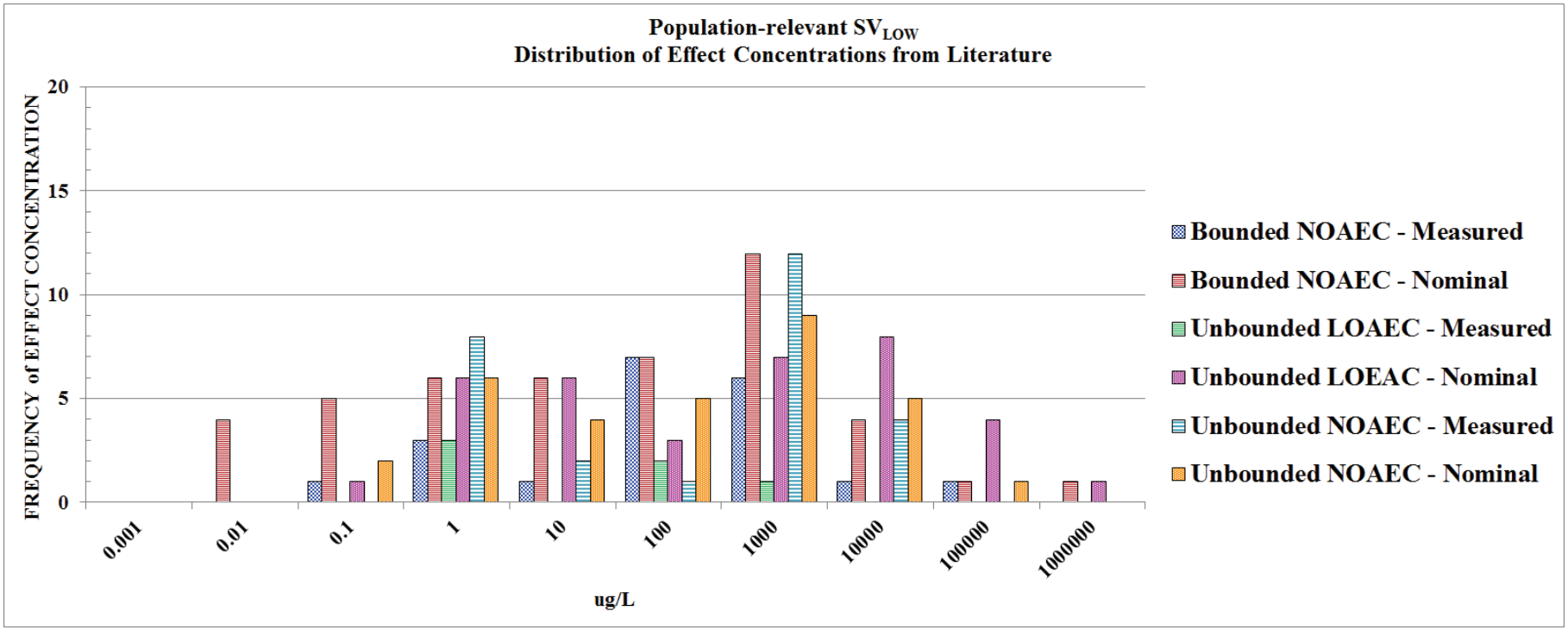


Figure 4-4 Distribution of unadjusted effect concentrations (ug/L) used to derive the population-relevant SV$_{LOW}$ point estimates (N = 167) for the 14 CECs included in this document. X-axis values are upper bounds of frequency distribution bin intervals.

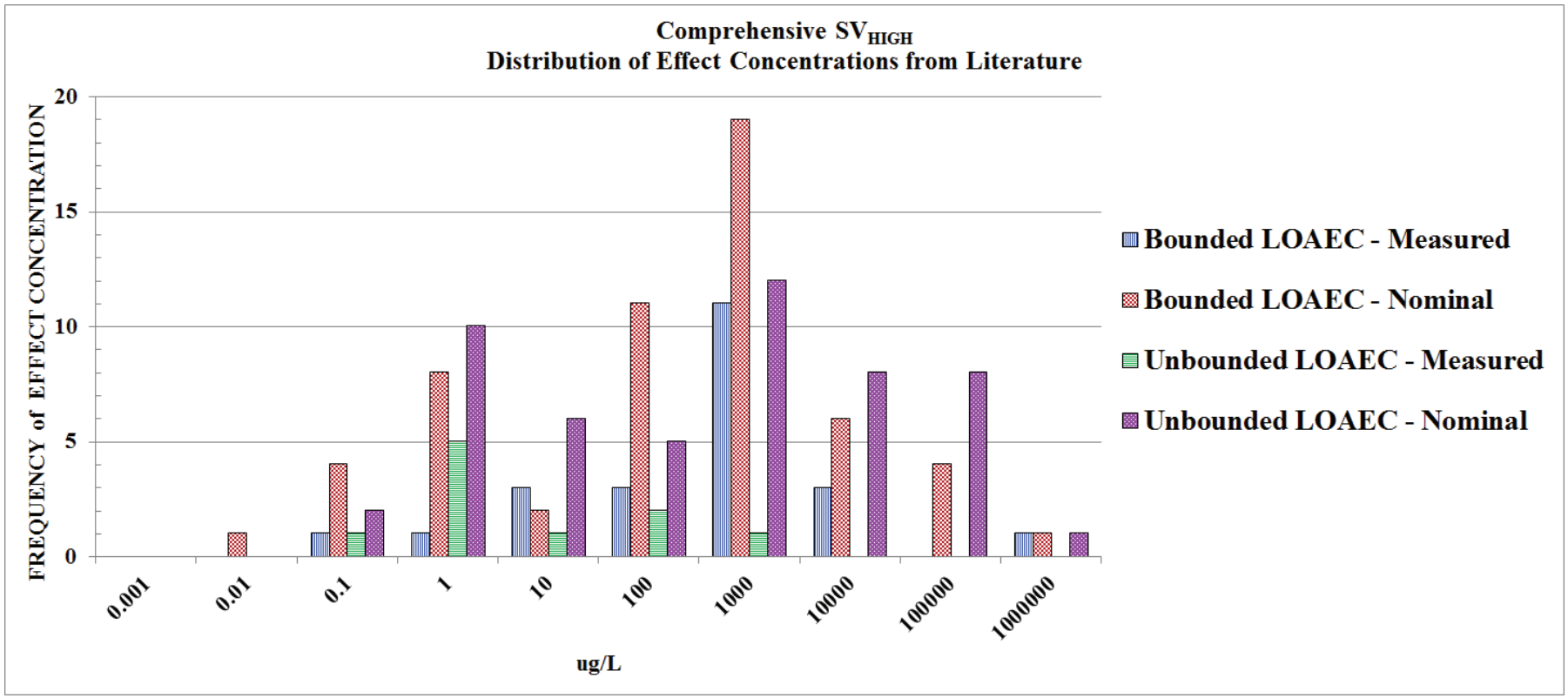


Figure 4-5. Distribution of unadjusted effect concentrations (ug/L) used to derive comprehensive type SVHIGH point estimates for the 14 CECs included in this document (N = 141). X-axis values are upper bounds of frequency distribution bin intervals

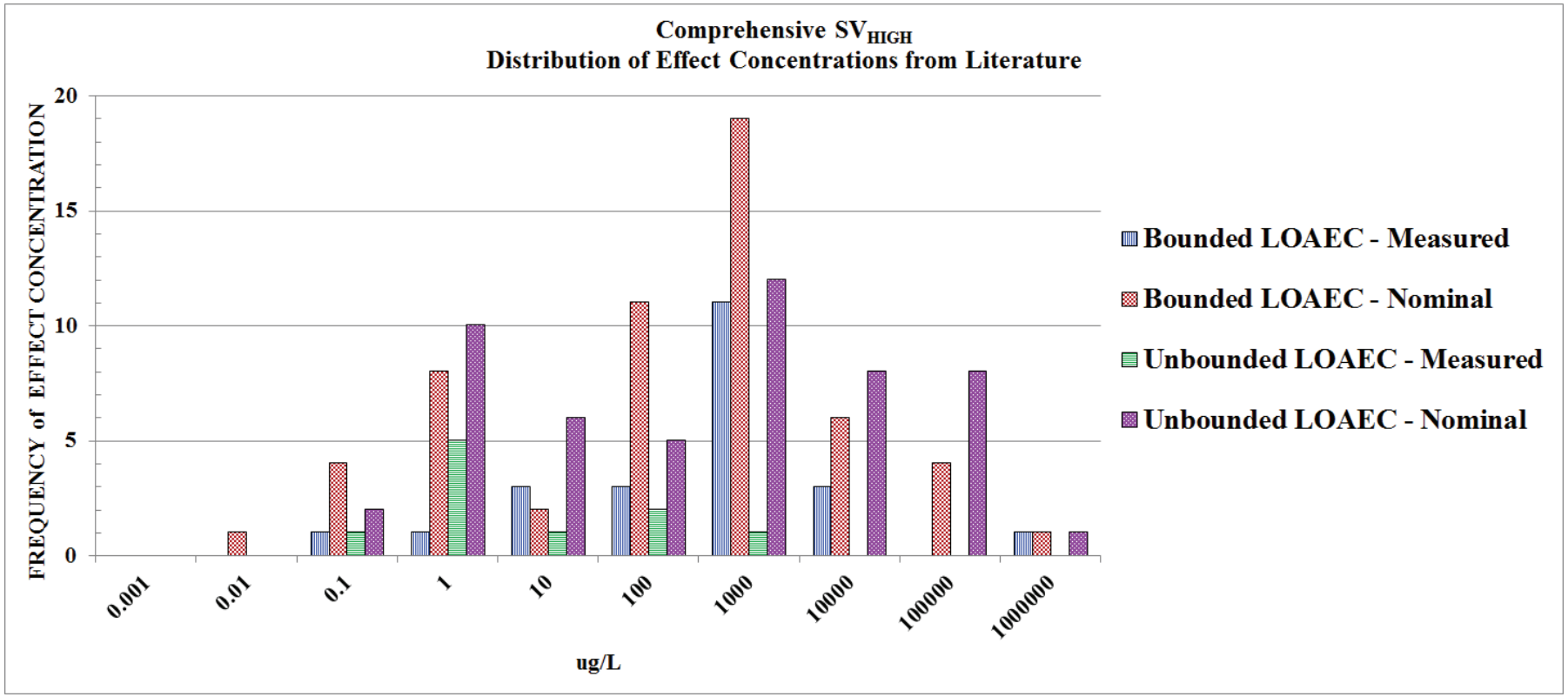


Figure 4-6. Distribution of effect concentrations (ug/L) used to derive the comprehensive type SV$_{LOW}$ point estimates (N = 214) for the 14 CECs included in this document. X-axis values are upper bounds of frequency distribution bin intervals.

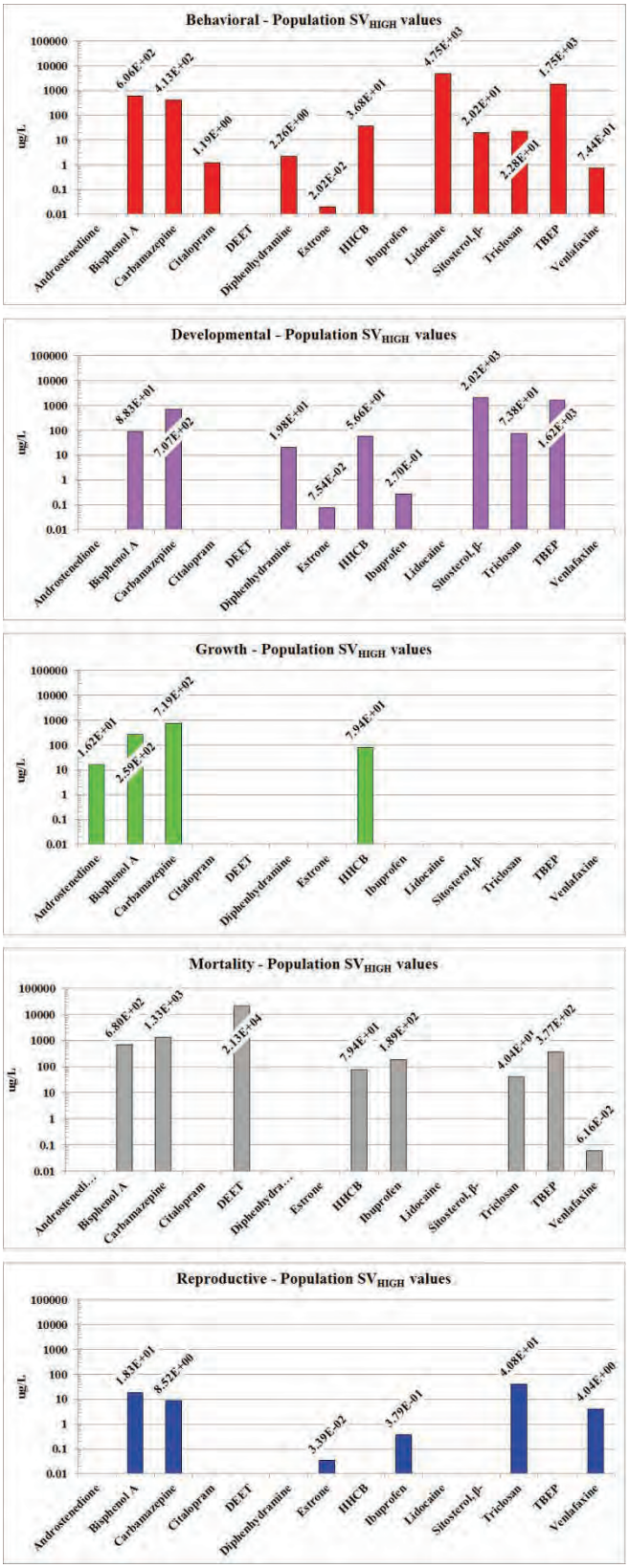


Figure 4-7. Effect-specific population-relevant SV$_{HIGH}$ values, by CEC.

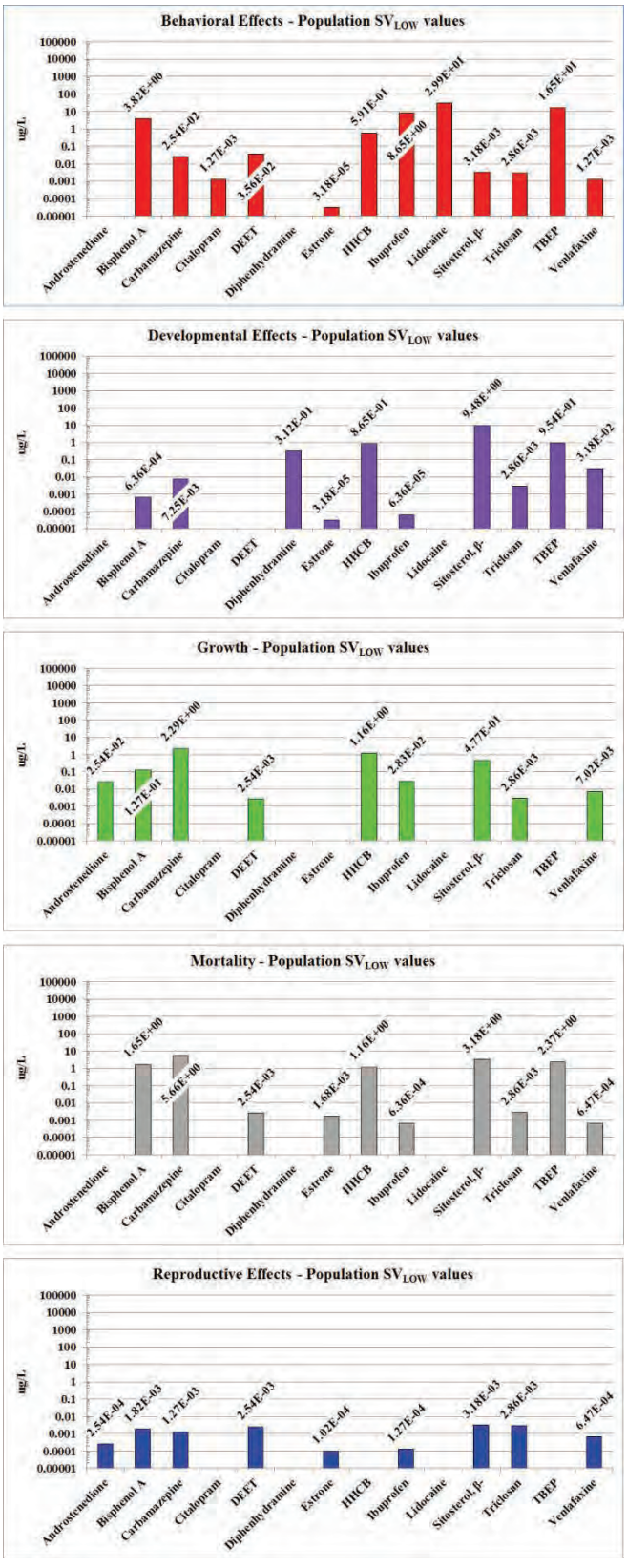


Figure 4-8. Effect-specific population-relevant SVLOW values, by CEC.

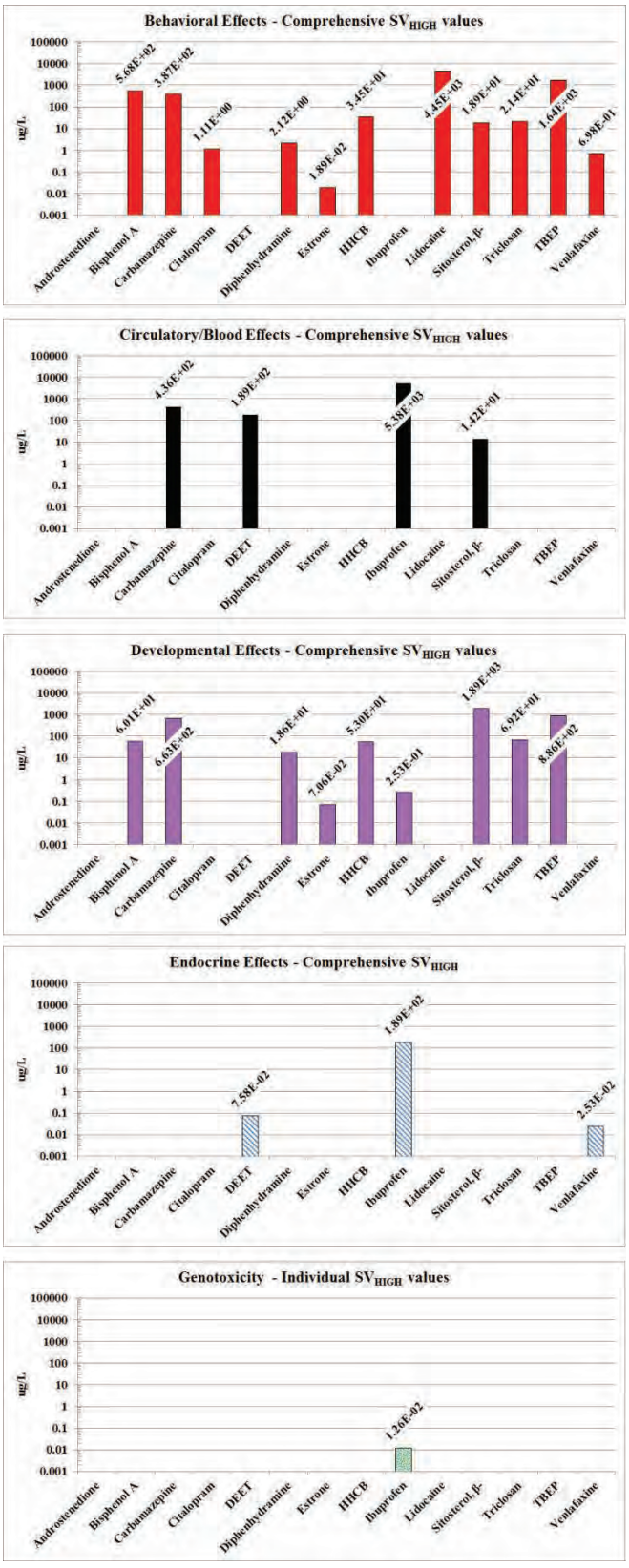


Figure 4-9. Effect-specific comprehensive SV$_{HIGH}$ values, by CEC.

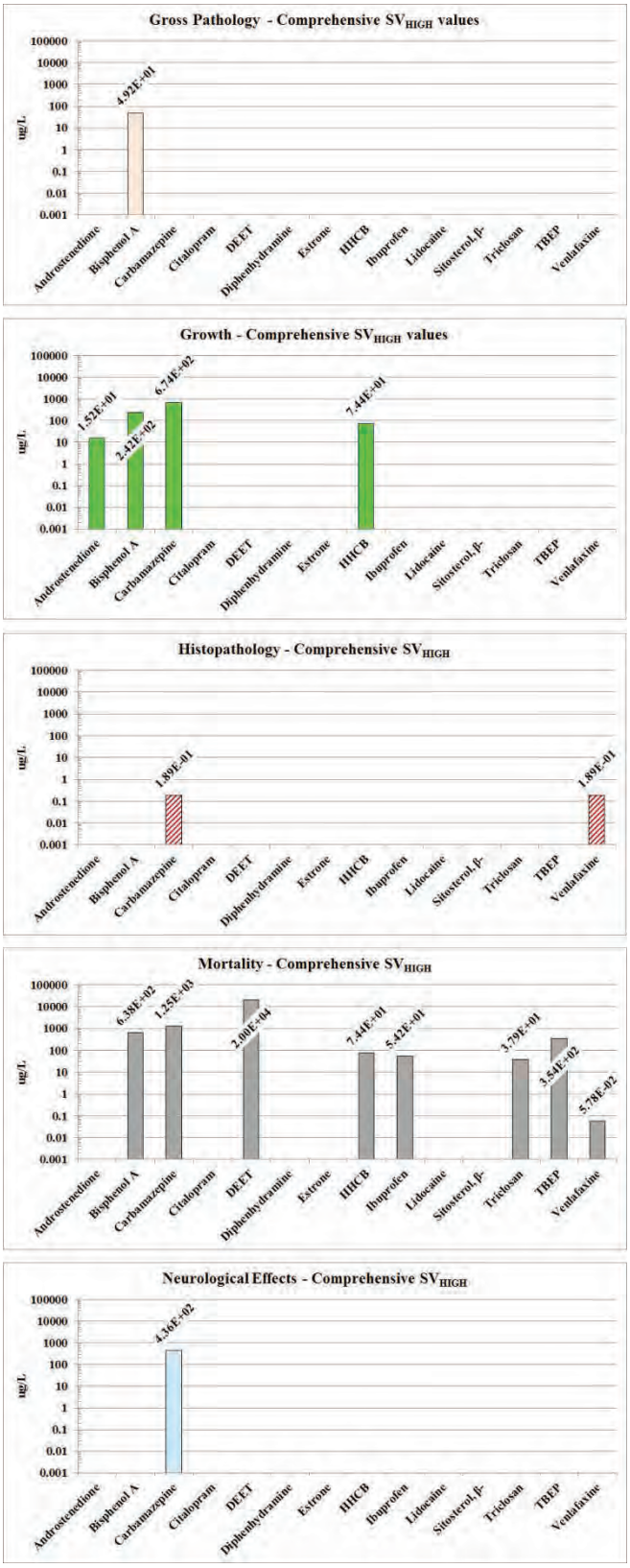


Figure 4-9 (continued). Effect-specific comprehensive SVHIGH values, by CEC.

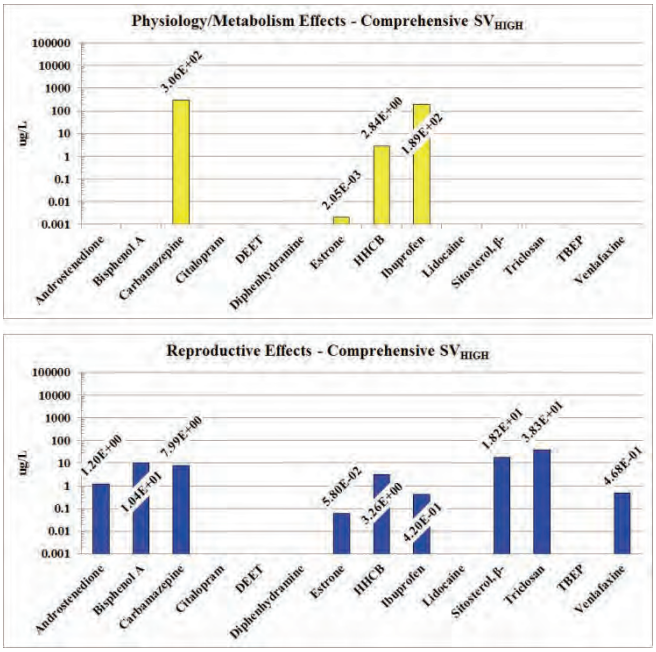


Figure 4-9 (continued). Effect-specific comprehensive SV$_{HIGH}$ values, by CEC.

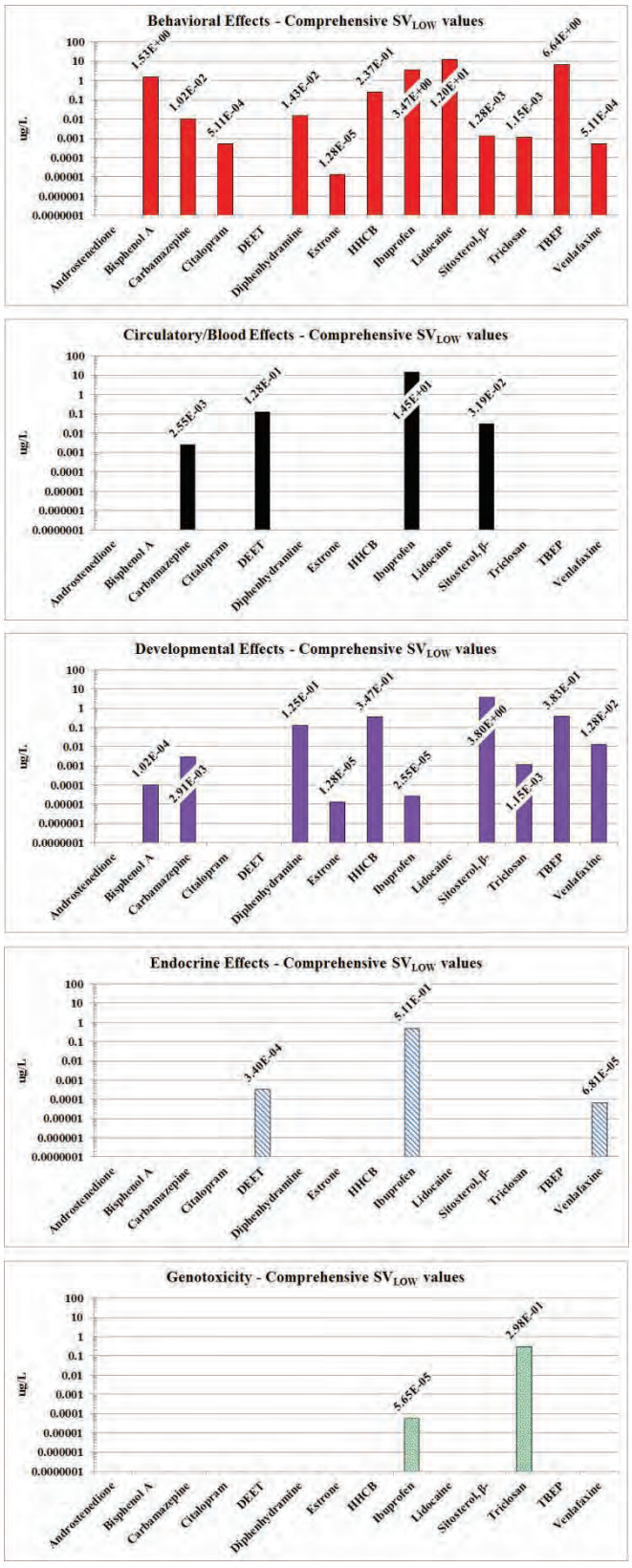


Figure 4-10. Effect-specific comprehensive SVLOW values, by CEC.

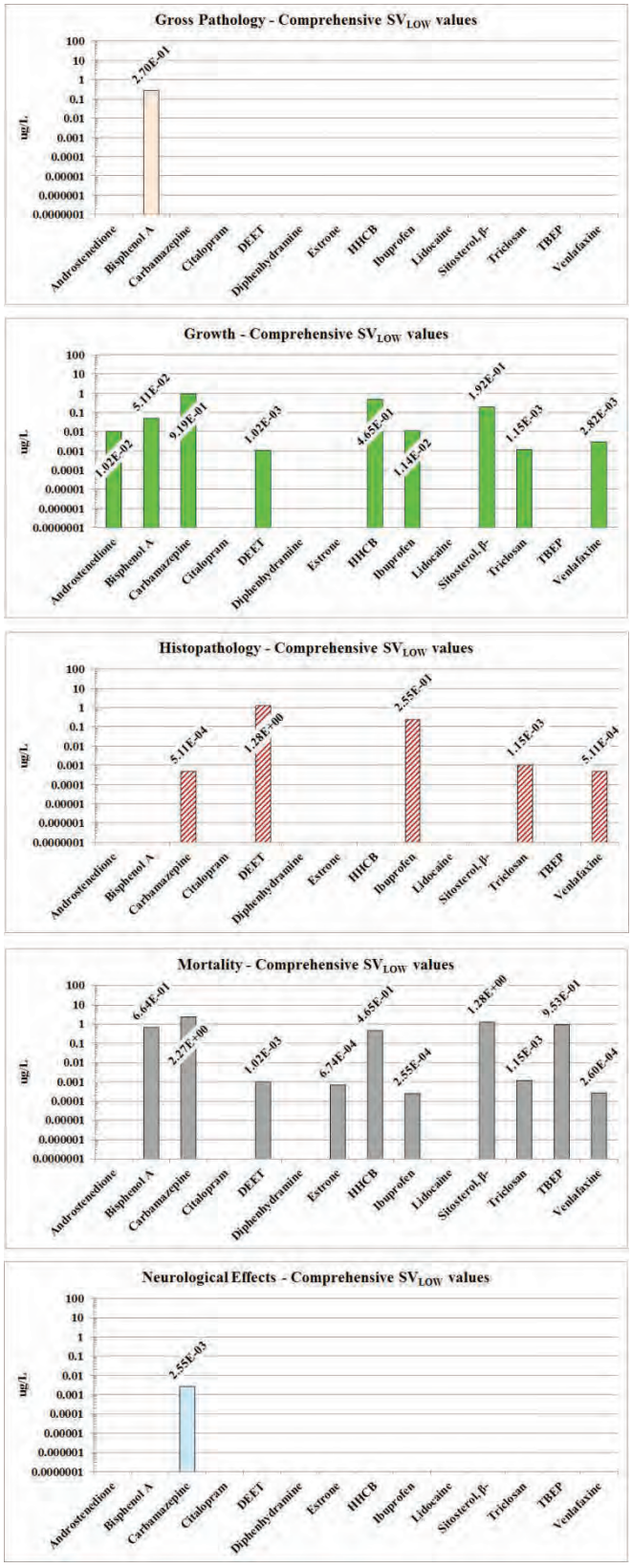


Figure 4-10 (continued). Effect-specific comprehensive SVLow values, by CEC.

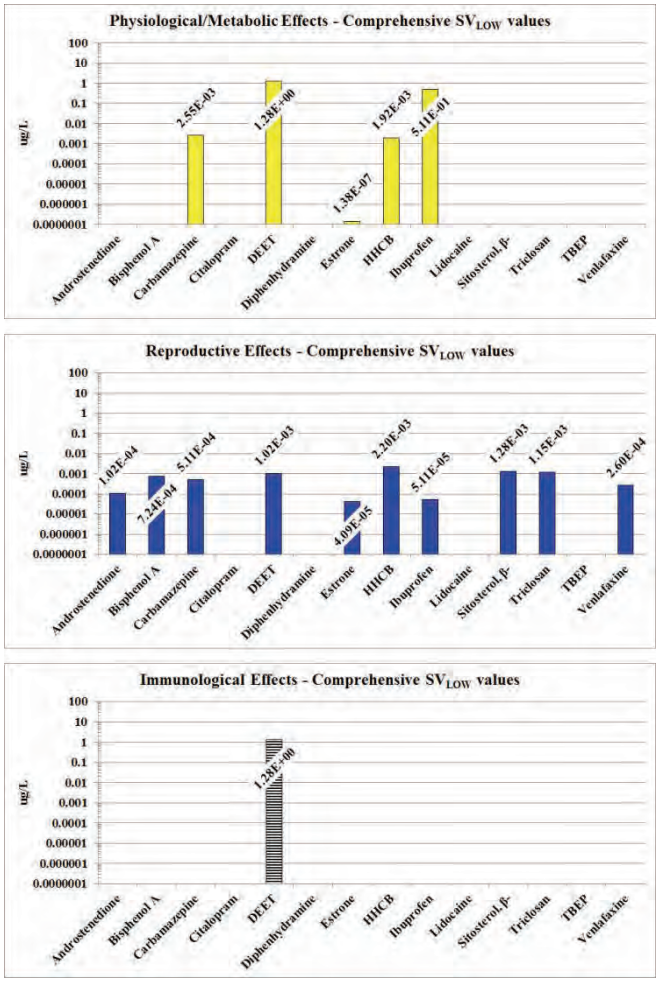


Figure 4-10 (continued). Effect-specific comprehensive SVLOW values, by CEC.

Table 4-1a. Population-relevant SV_{HIGH} values: Dissolved concentrations of CECs in surface water (ug/L) above which it is reasonable to expect adverse effects in freshwater fish populations, based on currently available published literature on CEC toxicity in fish (nd = no data). A blank cell indicates that data were not sufficient to generate an effect-specific SV estimate. The mean population-relevant SV_{HIGH} = (geometric mean of effect-specific SVs) / UF_{DATA}.

Chemical Name	Mean Population-relevant SV_{HIGH} (geometric mean of Effect-Specific SVs / UF_{DATA}) (ug/L)	Database Adequacy UF (UF_{DATA}) (Table 3-17)	Effect-Specific Population-relevant SV_{HIGH} Estimates (ug/L)				
			Behavioral	Developmental	Growth	Mortality	Reproductive
Androstene-3,17-dione, 4-	3.23E+00	5			1.62E+01		
Bisphenol A	1.77E+02	1	6.06E+02	8.83E+01	2.59E+02	6.80E+02	1.83E+01
Carbamazepine	2.99E+02	1	4.13E+02	7.07E+02	7.19E+02	1.33E+03	8.52E+00
Citalopram	2.37E-01	5	1.19E+00				
DEET	7.10E+03	3				2.13E+04	
Diphenhydramine	3.35E+00	2	2.26E+00	1.98E+01			
Estrone	1.86E-02	2	2.02E-02	7.54E-02			3.39E-02
HHCB	6.02E+01	1	3.68E+01	5.66E+01	7.94E+01	7.94E+01	
Ibuprofen	8.22E-01	2		2.70E-01		5.78E+01	2.85E-01
Lidocaine	9.49E+02	5	4.75E+03				
Sitosterol, β-	1.01E+02	2	2.02E+01	2.02E+03			
Triclosan	4.08E+01	1	2.28E+01	7.38E+01		4.04E+01	4.08E+01
TBEP	5.11E+02	2	1.75E+03	1.62E+03		3.77E+02	
Venlafaxine	2.85E-01	2	7.44E-01			6.16E-02	4.04E+00

Table 4-1b. Population-relevant SV_{LOW} values: Dissolved concentrations of CECs in surface water (ug/L) below which it is reasonable to expect no significant adverse effects in freshwater fish populations, based on currently available published literature on CEC toxicity in fish (nd = no data). A blank cell indicates that data were not sufficient to generate an effect-specific SV estimate. The mean population-relevant SV_{LOW} = (geometric mean of effect-Specific SVs) / UF_{DATA}.

Chemical Name	Mean Population-relevant SV_{LOW} (geometric mean of Effect-Specific SVs / UF_{DATA}) (ug/L)	Database Adequacy UF (UF_{DATA}) (Table 3-16)	Effect-Specific Population-relevant SV_{LOW} Estimates (ug/L)				
			Behavioral	Developmental	Growth	Mortality	Reproductive
Androstene-3,17-dione, 4-	1.27E-03	2			2.54E-02		2.54E-04
Bisphenol A	6.22E-02	1	3.82E+00	6.36E-04	1.27E-01	1.65E+00	1.82E-03
Carbamazepine	7.88E-02	1	2.54E-02	7.25E-03	2.29E+00	5.66E+00	1.27E-03
Citalopram	2.54E-04	5	1.27E-03				
DEET	1.27E-03	2			2.54E-03	2.54E-03	2.54E-03
Diphenhydramine	5.27E-02	2	3.56E-02	3.12E-01			
Estrone	1.15E-04	1	3.18E-05	3.18E-05		1.68E-03	1.02E-04
HHCB	9.10E-01	1	5.91E-01	8.65E-01	1.16E+00	1.16E+00	
Ibuprofen	4.17E-03	1	8.65E+00	6.36E-05	2.83E-02	6.36E-04	1.27E-04
Lidocaine	5.98E+00	5	2.99E+01				
Sitosterol, β-	1.71E-01	1	3.18E-03	9.48E+00	4.77E-01	3.18E+00	3.18E-03
Triclosan	2.86E-03	1	2.86E-03	2.86E-03	2.86E-03	2.86E-03	2.86E-03
TBEP	1.67E+00	2	1.65E+01	9.54E-01		2.37E+00	
Venlafaxine	2.60E-03	1	1.27E-03	3.18E-02	7.02E-03	6.47E-04	6.47E-04

Table 4-1c. Comprehensive SV_{HIGH} values: Dissolved concentrations of CECs in surface water (ug/L) above which it is reasonable to expect adverse effects in individuals of freshwater fish species, based on currently available published literature on CEC toxicity in fish. A blank cell indicates that data were not sufficient to generate an effect-specific SV estimate. The mean comprehensive SV_{HIGH} = (geometric mean of effect-specific SVs) / UF_{DATA}

Chemical Name	Mean Comprehensive SV_{HIGH} (geometric mean of Effect-Specific SVs / UF_{DATA})	Database Adequacy UF (UF_{DATA}) (Table 3-17)	Effect-Specific Comprehensive SV_{HIGH} Estimates (ug/L)												
			Behavioral	Circulatory/ Blood Constituents	Developmental	Endocrine	Genotoxicity	Gross Pathology	Growth	Histopathology	Immunological	Mortality	Neurological	Physiology/ Metabolism	Reproductive
Androstene-3,17-dione, 4-	8.52E-01	5							1.52E+01						1.20E+00
Bisphenol A	1.18E+02	1	5.68E+02		6.01E+01			4.92E+01	2.42E+02			6.38E+02			1.04E+01
Carbamazepine	1.39E+02	1	3.87E+02	4.36E+02	6.63E+02				6.74E+02	1.89E-01		1.25E+03	4.36E+02	3.06E+02	7.99E+00
Citalopram	2.22E-01	5	1.11E+00												
DEET	2.20E+01	3		1.89E+02		7.58E-02						2.00E+04			
Diphenhydramine	1.26E+00	5	2.12E+00		1.86E+01										
Estrone	6.65E-03	3	1.89E-02		7.06E-02									2.05E-03	5.80E-02
HHCB	2.13E+01	1	3.45E+01		5.30E+01				7.44E+01			7.44E+01		2.84E+00	3.26E+00
Ibuprofen	1.05E+01	1		5.38E+03	2.53E-01	1.89E+02	1.26E-02					5.42E+01		1.89E+02	4.20E-01
Lidocaine	8.90E+02	5	4.45E+03												
Sitosterol, β-	1.84E+01	3	1.89E+01	1.42E+01	1.89E+03										1.82E+01
Triclosan	1.28E+01	3	2.14E+01		6.92E+01							3.79E+01			3.83E+01
TBEP	2.67E+02	3	1.64E+03		8.86E+02							3.54E+02			
Venlafaxine	1.55E-01	1	6.98E-01			2.53E-02				1.89E-01		5.78E-02			4.68E-01

Table 4-1d. Comprehensive-type SVLOW values: Dissolved concentrations of CECs in surface water (ug/L) below which it is reasonable to expect no significant adverse effects in individuals of freshwater fish species, based on currently available published literature on CEC toxicity in fish. A blank cell indicates that data were not sufficient to generate an effect-specific SV estimate. The mean comprehensive SVLOW = (geometric mean of effect-specific SVs) / UFDATA.

Chemical Name	Mean Comprehensive SV_{LOW} (geometric mean of Effect-Specific SVs / UF_{DATA}) (ug/L)	Database Adequacy UF (UF_{DATA}) (Table 3-16)	Effect-Specific Comprehensive SV_{LOW} Estimates (ug/L)											
			Behavioral	Circulatory/ Blood Constituents	Developmental	Endocrine	Genotoxicity	Gross Pathology	Growth	Histopathology	Immunological	Mortality	Neurological	Physiology/ Metabolism	Reproductive
Androstene-3,17-dione, 4-	2.04E-04	5							1.02E-02						1.02E-04
Bisphenol A	3.18E-02	1	1.53E+00		1.02E-04			2.70E-01	5.11E-02			6.64E-01			7.24E-04
Carbamazepine	8.65E-03	1	1.02E-02	2.55E-03	2.91E-03				9.19E-01	5.11E-04		2.27E+00	2.55E-03	2.55E-03	5.11E-04
Citalopram	1.02E-04	5	5.11E-04												
DEET	2.36E-02	1		1.28E-01		3.40E-04			1.02E-03	1.28E+00	1.28E+00	1.02E-03		1.28E+00	1.02E-03
Diphenhydramine	8.46E-03	5	1.43E-02		1.25E-01										
Estrone	1.44E-05	1	1.28E-05		1.28E-05							6.74E-04		1.38E-07	4.09E-05
HHCB	6.49E-02	1	2.37E-01		3.47E-01				4.65E-01			4.65E-01		1.92E-03	2.20E-03
Ibuprofen	1.53E-02	1	3.47E+00	1.45E+01	2.55E-05	5.11E-01	5.65E-05		1.14E-02	2.55E-01		2.55E-04		5.11E-01	5.11E-05
Lidocaine	2.40E+00	5	1.20E+01												
Sitosterol, β-	6.04E-02	1	1.28E-03	3.19E-02	3.80E+00				1.92E-01			1.28E+00			1.28E-03
Triclosan	2.54E-03	1	1.15E-03		1.15E-03		2.98E-01		1.15E-03	1.15E-03		1.15E-03			1.15E-03
TBEP	4.48E-01	3	6.64E+00		3.83E-01							9.53E-01			
Venlafaxine	6.38E-04	1	5.11E-04		1.28E-02	6.81E-05			2.82E-03	5.11E-04		2.60E-04			2.60E-04

Table 4-2. List of fish species utilized in deriving CEC SVs. Niche, order, and family information was obtained from the FishBase on-line database on 12/18/2017; Genus and Species are recorded as provided in the CEC lab assay publications.

Order	Family	Scientific Name (Genus-Species)	Species Common Name	Ecological Niche	Species Resident in Great Lakes Basin?
Beloniformes	Adrianichthyidae	Oryzias latipes	Japanese medaka	Freshwater; brackish; benthopelagic; amphidromous	N
Beloniformes	Adrianichthyidae	Oryzias javanicus	Java medaka	Freshwater; brackish; benthopelagic; non-migratory	N
Beloniformes	Adrianichthyidae	Oryzias melastigma	Ricefish	Freshwater; brackish; benthopelagic; non-migratory	N
Cypriniformes	Cyprinidae	Carassius auratus	Goldfish	Freshwater; benthopelagic; non-migratory; potamodromous	Y
Cypriniformes	Cyprinidae	Cirrhinus mrigala	Indian major carp	Freshwater; demersal	N
Cypriniformes	Cyprinidae	Cyprinus carpio	Common carp	Freshwater; brackish; benthopelagic; non-migratory; potamodromous	Y
Cypriniformes	Cyprinidae	Danio rerio	Zebrafish	Freshwater; benthopelagic; non-migratory	N
Cypriniformes	Cyprinidae	Gobiocypris rarus	Rare minnow	Freshwater; benthopelagic; non-migratory	N
Cypriniformes	Cyprinidae	Pimephales promelas	Fathead minnow	Freshwater; demersal; non-migratory	Y
Cyprinodontiformes	Cyprinodontidae	Jordanella floridae	Flagfish	Freshwater; brackish; benthopelagic; non-migratory	N
Cyprinodontiformes	Poeciliidae	Poecilia reticulata	Guppy	Freshwater; brackish; benthopelagic; non-migratory	N
Cyprinodontiformes	Poeciliidae	Gambusia affinis	Mosquitofish	Freshwater; brackish; benthopelagic; potamodromous	N
Cyprinodontiformes	Poeciliidae	Xiphophorus helleri	Swordtail	Freshwater; brackish; benthopelagic; non-migratory	N

Table 4-2. (continued).

Order	Family	Scientific Name (Genus-Species)	Species Common Name	Ecological Niche	Species Resident in Great Lakes Basin?
Perciformes	Centrarchidae	Lepomis gibbosus	Pumpkinseed sunfish	Freshwater; brackish; benthopelagic; potamodromous	Y
Perciformes	Centrarchidae	Lepomis macrochirus	Bluegill	Freshwater; benthopelagic; non-migratory	Y
Perciformes	Gobiidae	Neogobius melanostomus	Round goby	Marine; freshwater; brackish; demersal; amphidromous	Y
Perciformes	Osphronemidae	Betta splendens	Beta fish; Siamese fighting fish	Freshwater; benthopelagic; non-migratory	N
Salmoniformes	Salmonidae	Oncorhynchus mykiss	Rainbow trout	Marine; freshwater; brackish; benthopelagic; anadromous	Y
Salmoniformes	Salmonidae	Salmo salar	Atlantic salmon	Marine; freshwater; brackish; benthopelagic; anadromous	Y
Salmoniformes	Salmonidae	Salmo trutta fario	Brown trout	Marine; freshwater; brackish; pelagic-neritic; anadromous	Y

Table 4-3. Rubric for assigning index of relative confidence in CEC-specific Mean SVs. The index value was based on representation of ecotoxicological information in the CEC Fish Ecotoxicity Database (as summarized by CEC in Section 4.4). Confidence Level Key: H = high; M = moderate; L = low; VL = very low; Gray Shaded = not applicable.

Number of Effect Categories Represented in the Fish Ecotoxicity Database	POPULATION-RELEVANT						COMPREHENSIVE TYPE									
		Number of Effect Categories with *More Than* 2 SV Point Estimates														
	0	1	2	3	4	5	0	1	2	3	4	5	6	7	8	>8
ONLY ONE FISH SPECIES is represented among Effect Categories																
1	VL	VL					VL	VL								
2	VL	VL	VL				VL	VL	VL							
3	VL	VL	L	L			VL	VL	VL	VL						
4	L	L	L	M	M		VL	VL	VL	VL	L					
5	L	L	M	M	M	M	VL	VL	VL	L	L	M				
6							L	L	L	L	M	M	M			
7							L	L	L	M	M	M	M	M		
8							L	L	M	M	M	M	M	H	H	
9							L	M	M	M	M	M	H	H	H	H
10							M	M	M	M	M	H	H	H	H	H
11							M	M	M	M	H	H	H	H	H	H
12							M	M	M	H	H	H	H	H	H	H
13							M	M	H	H	H	H	H	H	H	H
TWO or more FISH SPECIES are represented among Effect Categories																
1	VL	VL					VL	VL								
2	VL	L	L				VL	VL	VL							
3	VL	L	M	M			VL	VL	VL	VL						
4	VL	L	M	H	H		VL	VL	L	L	L					
5	L	M	H	H	H	H	VL	L	L	L	L	M				
6							L	L	M	M	M	M	H			
7							L	L	M	M	M	M	H	H		
8							M	M	M	M	M	H	H	H	H	
9							M	M	M	M	M	H	H	H	H	H
10							M	M	M	H	H	H	H	H	H	H
11							M	M	H	H	H	H	H	H	H	H
12							H	H	H	H	H	H	H	H	H	H
13							H	H	H	H	H	H	H	H	H	H

Literature Cited

(This section includes papers that are cited in Attachments)

Agency for Toxic Substances and Disease Registry (ATSDR). No date. Guidance for preparation of toxicological profiles. Centers for Disease Control, Department of Health and Human Services. Web page: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.

Ankley, G.T., K.M. Jensen, E.A. Makynen, M.D. Kahl, J.J. Korte, M.W. Hornung, T.R. Henry, J.S. Denny, R. Leino, V.S. Wilson, M.C. Cardon, P.C. Hartig and L.E. Gray. 2003. Effects of the androgenic growth promoter 17-b-trenbolone on fecundity and reproductive endocrinology of the fathead minnow. Environ Toxicol Chem 22(6): 1350-1360.

Armstrong, B.M., J.M. Lazorchak, C.A. Murphy, H.J. Haring, K.M. Jensen and M.E. Smith. 2015. Determining the effects of a mixture of an endocrine disrupting compound, 17a-ethinylestradiol, and ammonia on fathead minnow (*Pimephales promelas*) reproduction. Chemosphere 120: 108–114.

Arnot, J.A., D. Mackay, E. Webster and J.M. Southwood. 2006. Screening levels risk assessment model for chemical fate and effects in the environment. Environ Sci Technol 40(7): 2316-2323.

AXYS Analytical Services, Ltd. (AXYS). 2017. Pers. Comm. Unpublished Data. Spreadsheets of method detection limits and reporting limits for AXYS Analytical Services methods MLA-068, MLA-075, MLA-082, MLA-083, MLA-098.

Baldwin, D.H., J.A. Spromberg, T.K. Collier and N.L. Scholz. 2009. A fish of many scales: Extrapolating sublethal pesticide exposures to the productivity of wild salmon populations. Ecol Applic 19(8): 2004-2015.

Balk, F. and R.A. Ford. 1999. Environmental risk assessment for the polycyclic musks, AHTN and HHCB. II. Effect assessment and risk characterization. Toxicol Let 111: 81-94.

Barnes, D.G. and M. Dourson. 1988. Reference Dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8: 471-486.

Barnthouse, L.W., G.W. Suter II, A.E. Rosen and J.J. Beauchamp. 1987. Estimating responses of fish populations to toxic contaminants. Environ Toxicol Chem 6: 811-824.

Barnthouse, L.W., G.W. Suter, and A.E. Rosen. 1990. Risks of toxic contaminants to exploited fish population: Influence of life history, data uncertainty and exploitation intensity. Environ Toxicol Chem 9: 297-311. As cited in Calabrese and Baldwin (1995).

Bartell, S.M., R.A. Pastorok, H.R. Akcakaya, H. Regan, S. Ferson and C. Mackay. Realism and relevance of ecological models used in chemical risk assessment. Human Ecol Risk Assessm 9(4): 907-938.

Bearr, J.S., H.M. Stapleton and C.L. Mitchelmore. 2010. Accumulation and DNA damage in fathead minnows (Pimephales promelas) exposed to 2 brominated flame-retardant mixtures, Firemaster 550 and Firemaster BZ-54. Environ Toxicol Chem 29(3): 722-729.

Belanger, S.E., H. Sanderson, M.R. Enbry, K. Coady, D. DeZwart, BA. Farr, S. Gutsell, M. Hlder, R. Sternberg and P. Wilson. 2015. It is time to develop ecological thresholds of toxicological concern to assist environmental hazard assessment. Environ Toxicol Chem 34(12): 2864-2869.

Berninger, J.P. and B.W. Brooks. 2010. Leveraging mammalian pharmaceutical toxicology and pharmacology data to predict chronic fish responses to pharmaceuticals. Toxicol Lett 193: 69-78.

Berninger, J.P., E.S. Williams and B.W. Brooks. 2011. An initial probabilistic hazard assessment of oil dispersants approved by the United States National Contingency Plan. Environ Toxicol Chem 30(7): 1704-1708.

Best, C., N. Melnyk-Lamont, M. Gesto and M.M. Vijayan. 2014. Environmental levels of the antidepressant venlafaxine impact the metabolic capacity of rainbow trout. Aquat Toxicol 155: 190-198.

Brain, R.A., H. Sanderson, P.K. Sibley and K.R. Solomon. 2006. Probabilistic ecological hazard assessment: Evaluating pharmaceutical effects on aquatic higher plants as an example. Ecotoxicol Environ Safety 64(2): 128-135.

Brian, J.V., C.A. Harris, M. Scholze, T. Backhaus, P. Booy, M. Lamoree, G. Pojana, N. Jonkers, T. Runnalls, A. Bonfà, A. Marcomini and J.P. Sumpter. 2005. Accurate prediction of the response of freshwater fish to a mixture of estrogenic chemicals. Environ Health Perspectives 113(6): 721-728.

Brion, F., C.R. Tyler, X. Palazzi, B. Laillet, J.M. Porcher, J. Garric and P. Flammarion. 2004. Impacts of 17B-estradiol, including environmentally relevant concentrations, on reproduction after exposure during embryo-larval-, juvenile- and adult-life stages in zebrafish (Danio rerio). Aquat Toxicol 68: 193-217.

British Columbia Ministry of the Environment (BCME). 2009. Water quality guidelines for pharmaceutically-active-Compounds (PhACs): 17a-ethinylestradiol (EE2). Technical Appendix. Prepared by: N.K. Nagpal and C.L. Meays. Prepared for: Science and Information Branch, Water Stewardship Division, Ministry of the Environment.

Brown, A.R., A.M Riddle, N.L. Cunningham, T.J. Kedwards, N. Sillabeer and T.H. Hutchinson. 2003. Predicting the effects of endocrine disrupting chemicals on fish populations. Human Ecol Risk Assessm 9(3): 761-788.

Brown, A.R., L. Gunnarsson, E. Kristiansson and C. R. Tyler. 2014. Assessing variation in the potential susceptibility of fish to pharmaceuticals, considering evolutionary differences in their physiology and ecology. Phil Trans R Soc B 369: 20130576.

Brown, T.N. and F. Wania. 2008. Screening chemicals for the potential to be persistent organic pollutants: A case study of arctic contaminants. Environ Sci Technol, 42 (14): 5202–5209.

Calabrese, E.J. and L.A. Baldwin. 1994. A toxicological basis to derive a generic interspecies uncertainty factor. Environ Health Perspect 102(1): 14-17.

Calabrese, E.J. and L.A. Baldwin. 1995. A toxicological basis to derive generic interspecies uncertainty factors for application in human and ecological risk assessment. Hum Ecol Risk Assess 1(5): 555-564.

Caldwell, D.J., F. Mastrocco, T. Hutchinson, R. Lange, D. Heijerick, C. Janssen, P.D. Anderson, and J.P . Sumpter. 2008. Derivation of an aquatic predicted no-effect concentration for the synthetic hormone, 17a-ethinyl estradiol. Environ Sci Technol 42: 7046-7054.

Caldwell, D.J., F. Mastrocco, P.D. Anderson, R. Lange and J.P. Sumpter. 2012. Predicted-no-effect concentrations for the steroid estrogens estrone, 17b-estradiol, estriol, and 17a-ethinylestradiol. Environ Toxicol Chem 31(6): 1396-1406.

Capdevielle, M., R. Van Egmond, M. Whelan, D. Versteeg, M. Hofmann-Kamensky, J. Inauen, V. Cunningham and D. Woltering. 2008. Consideration of exposure and species sensitivity of triclosan in the freshwater environment. Integr Environ Assess Manage 4(1): 15-23.

Carlsson, C., A-K. Johansson, G. Alvan, K. Bergman and T. Kuhler. 2006. Are pharmaceuticals potent environmental pollutants? Part I: Environmental risk assessments of selected active pharmaceutical ingredients. Sci Total Environ 364: 67-87.

Carlsson, G. and L. Norrgren. 2004. Synthetic musk toxicity to early life stages of zebrafish (Danio rerio). Arch Environ Contam Toxicol 46: 102-105.

CAS (Chemical Abstract Society). 2015. CAS assigns the 100 millionth CAS Registry Number to a substance designed to treat acute myeloid leukemia. American Chemical Society Press Release dated 06/29/2015. Web Page: https://www.cas.org/news/media-releases/100-millionth-substance. Web Page accessed on 09-15-2016.

Cavallin, J.E., E.J. Durhan, N. Evans, K.M. Jensen, M.D. Kahl, D.W. Kolpin, E.P. Kolodziej, W.T. Foreman, C.A. Lalone, E.A.M. Akynen, S.M. Seidl, L.M. Thomas, D.L. Villeneuve, M.A. Weberg, V.S. Wilson and G.T. Ankley. 2014. Integrated assessment of runoff from livestock farming operations: Analytical chemistry, in vitro bioassays, and in vivo fish exposures. Environ Toxicol Chem 33(8): 1849-1857.

CCME (Canadian Council of Ministers of the Environment). 1999. Canadian water quality guidelines for the protection of aquatic life: Introduction. Web page: http://ceqg-rcqe.ccme.ca/download/en/312.

CCME. 2007a. Canadian water quality guidelines for the protection of aquatic life: A protocol for the derivation of water quality guidelines for the protection of aquatic life 2007. Web page: http://www.ccme.ca/files/Resources/supporting_scientific_documents/protocol_aql_2007e.pdf.

CCME. 2007b. Canadian environmental quality guidelines. Web page: http://www.ccme.ca/en/resources/canadian_environmental_quality_guidelines/. Web page accessed on 09/27/2016.

CECWG (Chemicals of Emerging Concern Working Group). 2009. Work Group report on chemicals of emerging concern. Prepared by: Chemicals of Emerging Concern Working Group. Prepared for: International Joint Commission. 15pp. http://www.ijc.org/files/publications/C220.pdf.

CECWG. 2011. Chemicals of emerging concern. Great Lakes Water Quality Agreement. 2009-2011 Priority Cycle Report. 25 pp. Prepared by: Chemicals of Emerging Concern Work Group. Prepared for: International Joint Commission.

Celander, M.C., J.V. Goldstone, N.D. Denslow, T. Iguchi, P. Kille, R.D. Meyerhoff, B.A. Smith, T.H. Hutchinson and J.R. Wheeler. 2011. Species extrapolation for the 21st century. Environ Toxicol Chem 30(1): 52-63.

Chapman, P.M. 2006. Emerging substances-emerging problems? Environ Toxicol Chem 25(6): 1445-1447.

Chapman, P.M. and R.S. Caldwell. 1996. A warning: NOECs are inappropriate for regulatory use. Environ Toxicol Chem 15(2): 77-79.

Chapman, P.M., A. Fairbrother and D. Brown. 1998. A critical evaluation of safety (uncertainty) factors for ecological risk assessment. Environ Toxicol Chem 17(1): 99–108.

Chen, F., J. Gao and Q. Zhou. 2012. Toxicity assessment of simulated urban runoff containing polycyclic musks and cadmium in Carassius auratus using oxidative stress biomarkers. Environ Pollut 162: 91-97.

Choy, S.J., M.L. Annis, J. Banda, S.R. Bowman, M.E. Brigham, S.M. Elliott, D.J. Gefell, M.D. Jankowski, Z.G. Jorgenson, K.E. Lee, J.N. Moore, and W.A. Tucker. 2017. Contaminants of emerging concern in the Great Lakes Basin: A report on sediment, water, and fish tissue chemistry collected in 2010-2012. U.S. Fish and Wildlife Service Biological Technical Publication No. BTP-R3001-2017. January, 2017.

Christianson-Heiska, I., P. Smeds, N. Granholm, E. Bergelin and B. Isomaa. 2007. Endocrine modulating actions of a phytosterol mixture and its oxidation products in zebrafish (*Danio rerio*). Compar Biochem Physiol Part C 145: 518-527.

Clotfelter, E.D. and A.C. Rodriguez. 2006. Behavioral changes in fish exposed to phytoestrogens. Environ Pollut 144: 833-839.

Coronado, M., H. De Haro, X. Deng, M.A. Rempel, R. Lavado and D. Schlenk. 2008. Estrogenic activity and reproductive effects of the UV-filter oxybenzone (2-hydroxy-4-methoxyphenyl-methanone) in fish. Aquat Toxicol 90: 182–187.

Correia, A.D., S. Freitas, M. Scholze, J.F. Gonçalves, P. Booij, M.H. Lamoree, E. Mañanós and M.A. Reis-Henriques. 2007. Mixtures of estrogenic chemicals enhance vitellogenic response in sea bass. Environ Health Perspectives 115(Suppl 1): 115-121.

Croudace, C.P., J.E. Caunter and P.A. Johnson. 1997. HHCB: Chronic toxicity to fathead minnow (*Pimephales promelas*) embryos and larvae. Report to RIFM, Zeneca Project Report BL5934/B. As cited in: Balk and Ford 1999.

Daughton, C.G. 2001. Pharmaceuticals in the environment: Overarching issues and overview. In Daughton, C.G. and T. Jones-Lepp (eds.) Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues. Symposium Series 791. American Chemical Society, Washington, D.C., pp 2-38. As cited in CECWG 2011.

Diamond, J.M., H.A. Latimer II, K.R. Munkittrick, K.W. Thornton, S.M. Bartell and K.A. Kidd. 2011. Prioritizing contaminants of emerging concern for ecological screening assessments. Environ Toxicol Chem 30(11): 2385-2394.

Dietrich, G.J., M. Żabowska, M. Wojtczak, M. Słowińska, D. Kucharczyk and A. Ciereszko. 2007. Effects of different surfactants on motility and DNA integrity of brown trout (*Salmo trutta fario*) and common carp (*Cyprinus carpio*) spermatozoa. Repro Biol 7(2): 127-142.

Dobbins, L.L., S. Usenko, R.A. Brain and B.W. Brooks. 2009. Probabilistic ecological hazard assessment of parabens using *Daphnia magna* and *Pimephales promelas*. 2009. Environ Toxicol Chem 28(12): 2744-2753.

DOE (Department of Energy). 1996. Toxicological benchmarks for screening potential contaminants of concern for effects on aquatic biota: 1996 Revision. Prepared by: Risk Assessment Program, Oak Ridge, TN. Authors: G.W. Suter, II, and C.L Tsao. Prepared for: U.S. DOE, Office of Environmental Management. Doc. No. ES/Em-96/R2.

Dourson, M.L. and J.F. Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol 3: 224-238.

Dourson, M.L., S.P. Felter and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul Toxicol Pharmacol 24: 108-120.

Dourson, M.L. and A.L. Parker. 2007. Past and future use of default assumptions and uncertainty factors: Default assumptions, misunderstandings, and new concepts. Human Ecol Risk Assessm 13: 82-87.

Duke, L.D. and M. Taggart. 2000. Uncertainty factors in screening ecological risk assessments. Environ Toxicol Chem 19(6): 1668–1680.

Duvall, S.E. and M.G. Barron. 2000. A screening level probabilistic risk assessment of mercury in Florida Everglades food webs. Ecotoxicol Environ Safety 47(3): 298-305.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 2010. Guidance on assessment factors to derive a DNEL. ECETOC Technical Report No. 110. ECETOC, Brussels, Belgium.

Elliott, S.M., M.E. Brigham, K.E. Lee, J.A. Banda, S.J. Choy, D.J. Gefell, T.A. Minarik, J.N. Moore and Z.G. Jorgenson. 2017. Contaminants of emerging concern in tributaries to the Laurentian Great Lakes: I. Patterns of occurrence. PLoS ONE 12(9): e0182868. https://doi.org/10.1371/journal.pone.0182868.

Ellis, L.D. and K.H. Soanes. 2012. A larval zebrafish model of bipolar disorder as a screening platform for neuro-therapeutics. Behav Brain res 233: 450-457.

Environment Canada/Health Canada (EC/HC). 2012. Preliminary Assessment. Triclosan. March 2012. Available at: http://www.ec.gc.ca/ese-ees/6EF68BEC-5620-4435-8729-9B91C57A9FD2/Triclosan_EN.pdf. As cited in Hull et al. 2015.

European Chemicals Bureau (ECB). 2003. Technical guidance document on risk assessment. Part II: Environmental Risk Assessment. Published by European Communities.

Fairchild, J.F., K.P. Feltz, L.C. Sappington, A.L. Allert, K.J. Nelson and J. Valle. 2009. An ecological risk assessment of the acute and chronic toxicity of the herbicide picloram to the threatened bull trout (*Salvelinus confluentus*) and the rainbow trout (*Onchorhyncus mykiss*). Arch Environ Contam Toxicol 56: 761–769.

Federle, T., P. Sun, S. Dyer and B. Kiel. (no date). Environmental Risk Assessment for the Polycyclic Musk, HHCB (1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran), in the United States. Prepared by: Procter & Gamble Company, Cincinnati, OH and International Flavors & Fragrances Ltd, Union Beach, NJ.

Ferrari, B., N. Paxeus, R. Lo Giudice, A. Pollio and J. Garric. 2003. Ecotoxicological impact of pharmaceuticals found in treated wastewaters: study of carbamazepine, clofibric acid, and diclofenac. Ecotoxicol Environ Safety 55: 359–370.

Ferrari, B., R. Mons, B. Vollat, B. Fraysse, N. Paxeus, R. Lo Giudice, A. Pollio and J. Garric. 2004. Environmental risk assessment of six human pharmaceuticals: Are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? Environ Toxicol Chem 23(5): 1344-1354.

Finn, J., M. Hui, V. Li, V. Lorenzi, N. de la Paz, S .H. Cheng, L. Lai-Chan and D. Schlenk. 2012. Effects of propranolol on heart rate and development in Japanese medaka (*Oryzias latipes*) and zebrafish (*Danio rerio*). Aquat Toxicol 122–123: 214-221.

Flinders, C.A., W.R. Streblow, R.E. Philbeck, D.L. Cook, D.E. Campbell, N.J. Brown-Peterson and T.S. Gross. 2014. Fathead minnow response to broad-range exposure of beta-sitosterol concentrations during life-cycle testing. Environ Toxicol Chem 33(2): 458-467.

Flippin, J.L., D. Huggett and C.M. Foran. 2007. Changes in the timing of reproduction following chronic exposure to ibuprofen in Japanese medaka, Oryzias latipes. Aquat Toxicol 81: 73-78.

Forbes, V.E., P. Calow, V. Grimm, T.I. Hayashi, T. Jager, A. Katholm, A. Palmqvist, R. Partorok, D. Salvito, R. Sibly, J. Spromberg, J. Stark and R.A. Stillman. 2011. Adding value to ecological risk assessment with population modeling. Human Ecol Risk Assessm 17: 287-299.

Forbes, V.E., N. Galic, A. Schmolke, J. Vavra, R. Pastorok and P. Thorbek. 2016. Assessing the risks of pesticides to threatened and endangered species using population modeling: A critical review and recommendations for future work. Environ Toxicol Chem 35(8): 1904-1913.

Galic, N., U. Hommen, J.M. Baveco and P.J. van den Brink. 2010. Potential application of population models in the European ecological risk assessment of chemicals. II. Review or models and their potential to address environmental protection aims. Integr Environ Assessm Manage 6(3): 338-360.

Galus, M., N. Kirischian, S. Higgins, J. Purdy, J. Chow, S. Rangaranjan, H. Li, C. Metcalfe, J.Y. Wilson. 2013a. Chronic, low concentration exposure to pharmaceuticals impacts multiple organ systems in zebrafish. Aquat Toxicol 132-133: 200-211.

Galus, M., J. Jeyaranjaan, E. Smith, H. Li, C. Metcalfe, J.Y. Wilson. 2013b. Chronic effects of exposure to a pharmaceutical mixture and municipal wastewater in zebrafish. Aquat Toxicol 132-133: 212-222.

Galus, M., S. Rangarajan, A. Lai, L. Shaya, S. Balshine and J.Y. Wilson. 2014. Effects of chronic, parental pharmaceutical exposure on zebrafish (*Danio rerio*) offspring. Aquat Toxicol 151: 124-134.

Gefell, D.J., M. Annis, J. Banda, A. Bellamy, S. Choy, S. Hummel, Z. Jorgenson, J.N. Moore, A.L. Secord and W.A. Tucker. 2019. Ecological Hazard Assessment of Contaminants of Emerging Concern in the U.S. Great Lakes Basin: Part A - Screening Assessment of Relative Hazard to Fish From Exposures to Contaminants of Emerging Concern in the Great Lakes Basin. U.S. Fish and Wildlife Service Biological Technical Publication. In Press.

Ginebreda, A., I. Muñoz, M. López de Alda, R. Brix, J. López-Doval and D. Barceló. 2009. Environmental risk assessment of pharmaceuticals in rivers: Relationships between hazard indexes and aquatic macroinvertebrate diversity indexes in the Llobregat River (NE Spain). Environ Internat 36(2): 153-162.

Hall, L.W., M.C. Scott and W.D. Killen. 1997. A screening level probabilistic ecological risk assessment of copper and cadmium in the Chesapeake Bay watershed. Prepared for: USEPA, Chesapeake Bay Program Office. Prepared by: Chesapeake Bay Program, Annapolis, MD. Final Report. September, 1997.

Hallgren, S. and K.H. Olsen. 2010. Effects on guppy brain aromatase activity following short-term steroid and 4-nonylphenol exposures. Environ Toxicol 25(3): 261-271.

Halling-Sorensen, B., H. Holten Lutzhoft, H.R. Andersen and F. Ingerslev. 2000. Environmental risk assessment of antibiotics: Comparison of mecillinam, trimethoprim and ciprofloxacin. J Antimicrob Chemotherapy 46(Suppl S1): 53-58.

Hamilton, P.B., I.G. Cowx, M.F. Oleksiak, A.M. Griffiths, M. Grahn, J.R. Stevens, G.R. Carvalho, E. Nicol and C.R. Tyler. 2016. Population-level consequences for wild fish exposed to sublethal concentrations of chemicals – a critical review. Fish Fisheries 17: 545-566.

Han, S., K. Choi, J. Kim, K. Ji, S. Kim, B. Ahn, J. Yun, K. Choi, J.S. Khim, X. Zhang and J.P. Giesy. 2010. Endocrine disruption and consequences of chronic exposure to ibuprofen in Japanese medaka (*Oryzias latipes*) and freshwater cladocerans Daphnia magna and Moina macrocopa. Aquat Toxicol 98: 256-264.

Han, X.B., K.W.Y. Yuen and R.S.S. Wu. 2013. Polybrominated diphenyl ethers affect the reproduction and development, and alter the sex ratio of zebrafish (*Danio rerio*). Environ Pollut 182: 120-126.

Han, Z., Q. Wang, J. Fu, H. Chen, Y. Zhao, B. Zhou, Z. Gong, S. Wei, J. Li, H. Liu, X. Zhang, C. Liu and H. Yu. 2014. Multiple bio-analytical methods to reveal possible molecular mechanisms of developmental toxicity in zebrafish embryos/larvae exposed to tris(2-butoxyethyl) phosphate. Aquat Toxicol 150: 175-181.

Hansen, P. 2007. Risk assessment of emerging contaminants in aquatic systems. Trends Anal Chem 26(11): 1095-1099.

Hanson, M.L. and K.R. Solomon. 2002. New t echnique for estimating thresholds of toxicity in ecological risk assessment. Environ Sci Technol 36: 3257-3264.

Harris, C.A., J.V. Brian, G. Pojana, M. Lamoree, P. Booy, A. Marcomini and J.P. Sumpter. 2009. The influence of a surfactant, linear alkylbenzene sulfonate, on the estrogenic response to a mixture of (xeno)estrogens in vitro and in vivo. Aquat Toxicol 91: 95-98.

Harris, C.A., P.B. Hamilton, T.J. Runnalls, V. Vinciotti, A. Henshaw, D. Hodgson, T.S. Coe, S. Jobling, S.R. Tyler and J.P. Sumpter. 2011. The consequences of feminization in breeding groups of wild fish. Environ Health Persp 119(3): 306-311.

Hazlerigg, C.R.E., C.R. Tyler, K. Lorenzen, J.R. Wheeler and P. Thorbek. 2014. Population relevance of toxicant mediated changes in sex ratio in fish: An assessment using an individual-based zebrafish (*Danio rerio*) model. Ecol Modelling 280: 76-88.

He, J., D. Yang, C. Wang,W. Liu, J. Liao ,T. Xu , C. Bai, J. Chen, K. Lin, C. Huang and Q. Dong. 2011. Chronic zebrafish low dose decabrominated diphenyl ether (BDE-209) exposure affected parental gonad development and locomotion in F1 offspring. Ecotoxicol 20: 1813-1822.

Health Canada/Environment Canada (HC/EC). 2012. Preliminary Assessment Triclosan. March, 2012.

Hegelund, T. K. Ottosson, M. RaDinger, P. Tomberg and M.C. Celander. 2004. Effects of the antifungal imidazole ketoconazole on CYP1A and CYP3A in rainbow trout and killifish. Environ Toxicol Chem 23(5): 1326–1334.

Hill, D.K. and J.J. Magnuson. 1990. Potential effects of global climate warming on the growth and prey consumption of Great Lakes fish. Trans N Amer Fish Soc 119: 265-275.

Hoekstra, J.A. and P.H. Van Ewijk. 1993. Alternatives for the no-observed-effect level. Environ Toxicol Chem 12: 187-194.

Holbech, H., K.L. Kinnberg, N. Brande-Lavridsen, P. Bjerregaard, G.I. Petersen, L. Norrgren, S. Örn, T. Braunbeck, L. Baumann, C. Bomke, M. Dorgerloh, E. Bruns, C. Ruehl-Fehlert, J.W. Green, T.A. Springer and A. Gourmelon. 2012. Comparison of zebrafish (*Danio rerio*) and fathead minnow (*Pimephales promelas*) as test species in the Fish Sexual Development Test (FSDT). Compar Biochem Physiol, Part C, 155: 407–415.

Holmberg, A., J. Fogel, E. Albertsson, J. Fick, J.N. Brown, N. Paceus, L. Forlin, J.I. Johnsson and D.G. Joakim Larsson. 2011. Does waterborne citalopram affect the aggressive and sexual behavior of rainbow trout and guppy? J Hazard Mater 187: 596-599.

Honkanen, J.O., A. Kostamo and J.V.K. Kukkonen. 2005. Toxicity of a phytosterol mixture to grayling (*Thymallus thymallus*) during early developmental stages. Arch Environ Contam Toxicol 48: 391-396.

Howard, P.H. and D.C.G. Muir. 2010. Identifying new persistent and bioaccumulative organics among chemicals in commerce. Environ Sci Technol 44: 2277-2285

Howard, P.H. and D.C.G. Muir. 2011. Identifying new persistent and bioaccumulative organics among chemicals in commerce II: Pharmaceuticals. Environ Sci Technol 45 (16): 6938-6946

Hua, Y.Z., L.G. Hua and Y.X. Fan. 2013. Single and combined effects of estrone and 17ß-estradiol on male goldfish. Biomed Environ Sci. 26(3): 176-184.

Hubbs, C.L. and K.F. Lagler. 2004. Fishes of the Great Lakes Region – Revised Edition. (Revised by G.R. Smith). The University of Michigan Press, Ann Arbor.

Hull, R.N., S. Kleywegt and J. Schroeder. 2015. Risk-based screening of selected contaminants in the Great Lakes Basin. J Gr Lakes Res 41: 238–245.

IJC (International Joint Commission). 2012. Great Lakes Water Quality Agreement, signed September 7, 2012. http://www.ec.gc.ca/grandslacs-greatlakes/A1C62826-72BE-40DB-A545-65AD6FCEAE92/1094_Canada-USA%20GLWQA%20_e.pdf

Ishibashi, H., N. Matsumura, M. Hirano, M. Matsuoka, H. Shiratsuchi, Y. Ishibashi, Y. Takao and K. Arizono. 2004. Effects of triclosan on the early life stages and reproduction of medaka *Oryzias latipes* and induction of hepatic vitellogenin. Aquat Toxicol 67: 167–179.

Ishibashi, H., M. Hirano, N. Matsumura, N. Watanabe, Y. Takao and K. Arizono. 2006. Reproductive effects and bioconcentration of 4-nonylphenol in medaka fish (*Oryzias latipes*). Chemosphere 65: 1019–1026.

Islas-Flores, H., L.M. Gomez-Olivan, M. Galar-Martinez, S. Garcia-Medina, N. Neri-Cruz and O. Dublan-Garcia. 2014. Effect of ibuprofen exposure on blood, gill, liver, and brain on common carp (*Cyprinus carpio*) using oxidative stress biomarkers. Environ Sci Pollut Res 21(7): 5157-5166.

IUCN (International Union for Conservation of Nature and Natural Resources). 2016. IUCN freshwater fish specialist group – freshwater fish diversity. Web Page: http://www.iucnffsg.org/freshwater-fishes/freshwater-fish-diversity/. Web page accessed on 09-15-2016.

Jager, T. 2012. Bad habits die hard: The NOEC's persistence reflects poorly on ecotoxicology. Environ Toxicol Chem 31(2): 228-229.

Ji, K., X. Liu, S. Lee, S. Kang, Y. Kho, J.P. Giesy and K. Choi. 2013. Effects of non-steroidal anti-inflammatory drugs on hormones and genes of the hypothalamic-pituitary-gonad axis, and reproduction of zebrafish. J Haz Mat 254-255: 242– 251.

Jobling, S., D. Casey, T. Rodgers-Gray, J. Oehlmann, U. Schulte-Oehlmann, S. Pawlowski, T. Baunbeck, A.P. Turner and C.R. Tyler. 2004. Comparative responses of molluscs and fish to environmental estrogens and an estrogenic effluent. Aquat Toxicol 65: 205-220.

Jordan, J., A. Zare, L.J. Jackson, H.R. Habibi and A.M. Weljie. 2012. Environmental contaminant mixtures at ambient concentrations invoke a metabolic stress response in goldfish not predicted from exposure to individual compounds alone. J Proteome Res 11: 1133-1143.

Jukosky, J.A., M.C. Watzin and J.C. Leiter. 2008. The effects of environmentally relevant mixtures of estrogens on Japanese medaka (*Oryzias latipes*) reproduction. Aquat Toxicol 86: 323–331.

Kadry, A.M., G.A. Skowronski and M.S. Abdel-Rahman. 1995. Evaluation of the use of uncertainty factors in deriving RfDs for some chlorinated compounds. J Toxicol Environ Health 45: 83-95.

Keiter, S., L. Baumann, H. Färber, H. Holbech, D. Skutlarek, M. Engwall and T. Braunbeck. 2012. Long-term effects of a binary mixture of perfluorooctane sulfonate (PFOS) and bisphenol A (BPA) in zebrafish (*Danio rerio*). Aquat Toxicol 118–119: 116–129.

Kenaga, E.E. 1982. Predictability of chronic toxicity from acute toxicity of chemicals in fish and aquatic invertebrates. Environ Toxicol Chem I: 347-358.

Kiparissis, Y., T.L. Metcalfe, G.C. Balch and C.D. Metcalfe. 2003. Effects of the antiandrogens, vinclozolin and cyproterone acetate on gonadal development in the Japanese medaka (*Oryzias latipes*). Aquat Toxicol 63: 391-403.

Kooijman, S.A.L.M., J.J.M. Bedaux and W. Slob. 1996. No-effect concentration as a basis for ecological risk assessment. Risk Anal 16: 445-447.

Kuo, Y.-M., M.S. Sepulveda, T.M. Sutton, H.G. Ochoa-Acuna, A.M. Muir, B. Miller and I. Hua. 2010. Bioaccumulation and biotransformation of decabromodiphenyl ether and effects on daily growth in juvenile lake whitefish (*Coregonus clupeaformis*). Ecotoxicol 19: 751–760.

Kwak, H-I., MO. Bae, M-H. Lee, Y-S. Lee, B-J. Lee, K-S. Kang, C-H. Chae, H-J. Sung, J-S. Shin, J-H. Kim, W-C. Mar, Y-Y. Sheen and M-H. Cho. 2001. Effects of nonylphenol, Bisphenol A, and their mixture on the viviparous swordtail fish (*Xiphophorus helleri)*. Environ Toxicol Chem 20(4): 787–795.

Lalone, C.A., D.L. Villeneuve, J.E. Cavallin, M.D. Kahl, E.J. Durhan, E.A. Makynen, K.M. Jensen, K.E. Stevens, M.N. Severson, C.A. Blanksma, K.M. Flynn, P.C. Hartig, J.S. Woodard, J.P. Berninger, T .J. Norberg-King, R.D. Johnson and G.T. Ankley. 2013. Cross-species sensitivity to a novel androgen receptor agonist of potential environmental concern, spironolactone. Environ Toxicol Chem 32(11): 2528–2541.

Landis, W.G. and P.M. Chapman. 2011. Well past time to stop using NOELs and LOELs. Integr Environ Assessm Manage 7(4): vi-viii.

Lange, R., T.H. Hutchinson, N. Scholz and J. Solbe. 1998. Analysis of the ECETOC Aquatic Toxicity (EAT) Database II – Comparison of acute to chronic ratios for various aquatic organisms and chemical substances. Chemosphere 36(1): 115-127.

Lange, R., T.H. Hutchinson, C.P. Croudace, F. Siegmund, H. Schweinfurth, P. Hampe, G.H. Panter and J.P. Sumpter. 2001. Effects of the synthetic estrogen 17a-ethinylestradiol on the life-cycle of the fathead minnow (*Pimephales promelas*). Environ Toxicol Chem 20(6): 1216–1227.

Lange, A., Y. Katsu, S. Miyagawa, Y. Ogino, H. Urushitani, T. Kobayashi, T. Hirai, J.A. Shears, M. Nagae, J. Yamamoto, Y. Ohnishi, T. Oka, N. Tatarazako, Y. Ohta, C.R. Tyler and T. Iguchi. 2012. Comparative responsiveness to natural and synthetic estrogens of fish species commonly used in the laboratory and field monitoring. Aquat Toxicol 109: 250– 258.

Laskowski, R. 1995. Some good reasons to ban the use of NOEC, LOEC and related concepts in ecotoxicology. Oikos 73: 140-144.

Lee, K.E., S.K. Langer, M.A. Menheer, W.T. Foreman, E.T. Furlong, and S. Smith. 2012. Chemicals of emerging concern in water and bottom sediment in Great Lakes areas of concern, 2010 to 2011—Collection methods, analyses methods, quality assurance, and data. USGS Data Series 723. 26 pp. Prepared in cooperation with the U.S. Fish and Wildlife Service and the U.S. Environmental Protection Agency.

Lee, K.E., S.K. Langer, M.A. Menheer, D.S. Hansen, W.T. Foreman, E.T. Furlong, Z.G. Jorgenson, S.J. Choy, J.N. Moore, J.A. Banda and D.J. Gefell. 2015. Chemicals of emerging concern in water and bottom sediment in the Great Lakes Basin, 2012—Collection methods, analytical methods, quality assurance, and study data: U.S. Geological Survey Data Series 910. 14 pp. Prepared in cooperation with the U.S. Fish and Wildlife Service and the U.S. Environmental Protection Agency. http://dx.doi.org/10.3133/ds910.

Lei, B., Y. Wen, X. Wang, J. Zha, W. Li, Z. Wang, Y. Sun, J. Kang and Y. Wang. 2013. Effects of estrone on the early life stages and expression of vitellogenin and estrogen receptor genes of Japanese medaka (*Oryzias latipes*). Chemosphere 93: 1104–1110.

Lei, B., J. Kang, Y. Yu, J. Zha, W. Li, Z. Wang, Y. Wang and Y.Wen. 2014. Long-term exposure investigating the estrogenic potency of estriol in Japanese medaka (*Oryzias latipes*). Compar Biochem Physiol Part C 160: 86-92.

Lin, L.L. and D.M. Janz. 2006. Effects of binary mixtures of xenoestrogens on gonadal development and reproduction in zebrafish. Aquat Toxicol 80: 382–395.

Liu, X., K. Ji and K. Choi. 2012. Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat Toxicol 114-115: 173– 181.

MacLatchy, D., L. Peters, J. Nickle and G. Van der Kraak. 1997. Exposure to B-sitosterol alters the endocrine status of goldfish differently than 17B-estradiol. Environ Toxicol Chem 16(9): 1895–1904.

Madureira, T.V., C. Cruzeiro, M.J. Rocha and E. Rocha. 2011a. The toxicity potential of pharmaceuticals found in the Douro River estuary (Portugal)—Experimental assessment using a zebrafish embryo test. Environ Toxicol Pharmacol 32: 212–217.

Madureira, T.V., M.J. Rocha, C. Cruzeiro, M.H. Galante, R.A.F. Monteiro and E. Rocha. 2011b. The toxicity potential of pharmaceuticals found in the Douro River estuary (Portugal): Assessing impacts on gonadal maturation with a histopathological and stereological study of zebrafish ovary and testis after sub-acute exposures. Aquat Toxicol 105: 292–299.

Madureira, T.V., M.J. Rocha, C. Cruzeiro, I. Rodrigues, R.A.F. Monteiro and E. Rocha. 2012. The toxicity potential of pharmaceuticals found in the Douro River estuary (Portugal): Evaluation of impacts on fish liver, by histopathology, stereology, vitellogenin and CYP1A immunohistochemistry, after sub-acute exposures of the zebrafish model. Environ Toxicol Pharmacol 34: 34–45.

Mandich, A., S. Bottero, E. Benfenati, A. Cevasco, C. Erratico, S. Maggioni, A. Massari, F. Pedemonte, L. Viganò. 2007. *In vivo* exposure of carp to graded concentrations of bisphenol A. Gen Compar Endocrinol 153: 15–24.

Marty, M.S., A. Blankinship, J. Chambers, L. Constantine, W. Kloas, A. Kumar, L. Lagadic, J. Meador, D. Pickford, T. Schwarz and T. Verslycke. 2016. Population-relevant endpoints in the evaluation of endocrine-active substances (EAS) for ecotoxicological hazard and risk assessment. Integr Environ Assessm Manage 13(2): 317-330.

Matson, C.W., A.R. Timme-Laragy and R.T. DiGiulio. 2008. Fluoranthene, but not benzo(a)pyrene, interacts with hypoxia resulting in pericardial effusion and lordosis in developing zebrafish. Chemosphere 74: 149-154.

Mayer, F.L., G.F. Krause, D.R. Buckler, M.R. Ellersieke and G. Lee. 1994. Predicting chronic lethality of chemicals to fishes from acute toxicity test data: Concepts and linear regression analysis. Environ Toxicol Chem 13(4): 671-678.

Mayo-Bean, K., K. Moran-Bruce, J.V. Nabholz, W.M. Meylan and P.H. Howard. 2012. Operational Manual for the Ecological Structure-Activity Relationship Model (ECOSAR) Class Program: MS-Windows Version 1.11. Risk Assessment Division, USEPA, Washington, D.C. March, 2012. Web page accessed on 09/21/2016: https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

McGee, M.R., M.L. Julius, A.M. Vajda, D.O. Norris, L.B. Barber and H.L. Schoenfuss. 2009. Predator avoidance performance of larval fathead minnows (*Pimephales promelas*) following short-term exposure to estrogen mixtures. Aquat Toxicol 91: 355–361.

McKim, J.M. 1977. Evaluation of tests with early life stages of fish for predicting long-term toxicity. J Fish Res Board Canada 34(8): 1148-1154.

Metcalfe, C.D., T.L. Metcalfe, Y. Kiparissis, B.G. Koenig, C. Khan, R.J. Hughes, T.R. Croley, R.E. March And T. Potter. 2001. Estrogenic potency of chemicals detected in sewage treatment plant effluents as determined by in vivo assays with Japanese medaka (*Oryzias latipes*). Environ Toxicol Chem 20(2): 297–308.

Michael, A.G. and G.S. Grant. 1974. Toxicity of the repellent DEET (N,N-diethyl-meta-toluamide) to *Gambusia affinis* (Baird and Girard). Mosquito News 34(1): 32-34.

Mihaich, E., J. Rhodes, J. Wolf, N. Van der Hoeven, D. Dietrich, A.T. Hall, N. Caspers, L. Ortego, C. Staples, S. Dimond and S. Hentges. 2012. Adult fathead minnow, *Pimephales promelas*, partial life-cycle reproductive and gonadal histopathology study with Bisphenol A. Environ Toxicol Chem 31(11): 2525–2535.

Ministry of Environment and Energy (MOEE). 1994. Policies, Guidelines, Provincial Water Quality Objectives of the Ministry of Environment and Energy. Ontario, Canada. ISBN 0-7778-8473-9 rev. Reprinted 1999, Queen's Printer for Ontario.

Morthorst, J.E., A. Lister, P. Bjerregaard and G. Van Der Kraak. 2013. Ibuprofen reduces zebrafish PGE2 levels but steroid hormone levels and reproductive parameters are not affected. Compar Biochem Physiol Part C 157: 251-257.

NAS (National Academy of Sciences). 2013. Assessing risks to endangered and threatened species from pesticides. Prepared by: Committee on Ecological Risk Assessment under FIFRA and ESA, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. The National Academy Press, Washington, D.C.

NLM (National Library of Medicine). 2016. TOXLINE on-line database. Department of Health and Human Services, National Institutes of Health, U.S. National Library of Medicine. Web page accessed on 09/21/2016: https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE

New York State Department of Environmental Conservation (NYSDEC). 2016. Water quality standards for taste-, color- and odor-producing, toxic and other deleterious substances. 6 CRR-NY 703.5. Current through 15 August, 2016. Web Page: https://govt.westlaw.com/nycrr/Document/I4ed90418cd1711dda432a117e6e0f345?viewType=FullText&originationContext=documenttoc&transitionType=CategoryPageItem&contextData=(sc.Default).

Oakes, K.D., P.K. Sibley, J.W. Martin, D.D. Maclean, K.R. Solomon, S.A. Mabury and G.J. Van der Kraak. 2005. Short-term exposures of fish to perfluorooctane sulfonate: Acute effects on fatty acyl–CoA oxidase activity, oxidative stress, and circulating sex steroids. Environ Toxicol Chem 24(5): 1172–1181.

Organisation for Economic Co-operation and Development (OECD). 2008. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 95: Detailed review paper on fish life-cycle tests. OECD Doc. No. ENV/JM/MONO(2008)22. Prepared by OECD Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. July, 2008.

Oehlmann, J., M. Oetken and U. Schulte-Oehlmann. 2008. A critical evaluation of the environmental risk assessment for plasticizers in the freshwater environment in Europe, with special emphasis on bisphenol A and endocrine disruption. Environ Res 108: 140-149.

Oliveira, R., I. Domingues, C.K. Grisolia and A.M.V.M. Soares. 2009. Effects of triclosan on zebrafish early-life stages and adults. Environ Sci Pollut Res 16: 679-688.

Olsen, K.H., K. Ask, H. Olsen, I. Porsch-Hallstrom and S. Hallgren. 2014. Reprint of "Effects of the SSRI citalopram on behaviours connected to stress and reproduction in Endler guppy, *Poecilia wingei*. Aquat Toxicol 151: 97-104.

Orn, S., S. Yamani and L. Norrgren. 2006. Comparison of vitellogenin induction, sex ratio, and gonad morphology between zebrafish and Japanese medaka after exposure to 17alpha-ethinylestradiol and 17beta-trenbolone. Arch Environ Contam Toxicol 51(2): 237-243.

Orrego, R., J. Guchardi, L. Beyger, R. Krause and D. Holdway. 2011. Comparative embryotoxicity of pulp mill extracts in rainbow trout (*Oncorhynchus mykiss*), American flagfish (Jordanella floridae) and Japanese medaka (*Oryzias latipes*). Aquat Toxicol 104: 299–307.

Painter, M.M., M.A. Buerkley, M.L. Julius, A.M. Vajda, D.O. Norris, L.B. Barber, E.T. Furlong, M.M. Schultz and H.L. Schoenfuss. 2009. Antidepressants at environmentally relevant concentrations affect predator avoidance behavior of larval fathead minnows (*Pimephales promelas*). Environ Toxicol Chem 28(12): 2677–2684.

Panter, G.H., T.H. Hutchinson, K.S. Hurd, A. Sherren, R.D. Stanley and C.R. Tyler. 2004. Successful detection of (anti-)androgenic and aromatase inhibitors in pre-spawning adult fathead minnows (*Pimephales promelas*) using easily measured endpoints of sexual development. Aquat Toxicol 70: 11-21.

Park, I., S.J. Park, H.W. Gil, Y.K. Nam and D.S. Kim. 2011. Anesthetic effects of clove oil and lidocaine-HCl on marine medaka (O*ryzias dancena*). Lab Animal 40(2): 45-51.

Park, S. and K. Choi. 2008. Hazard assessment of commonly used agricultural antibiotics on aquatic ecosystems. Ecotoxicol 17: 526-538.

Parrish, P.R., E.E. Dyar, J.M. Enos and W.G. Wilson. 1978. Chronic toxicity of chlordane, trifluralin, and pentachlorophenol to sheepshead minnows (*Cyprinodon variegatus*). USEPA, ORD, Environmental Research Laboratory, Doc. No. EPA-600/3-78-010.

Parrott, J.L. and D.T. Bennie. 2009. Life-cycle exposure of fathead minnows to a mixture of six common pharmaceuticals and triclosan. J Toxicol Environ Health (Part A) 72: 633–641.

Pastorok, R.A., H.R. Akcakaya, H. Regan, S. Ferson and S.M. Bartell. 2003. Role of ecological modeling in risk assessment. Human Ecol Risk Assessm 9(4): 939-972.

Paulos, P., T.J. Runnalls, G. Nallani, T. La Point, A.P. Scott, J.P. Sumpter and D.B. Huggett. 2010. Reproductive responses in fathead minnow and Japanese medaka following exposure to a synthetic progestin, norethindrone. Aquat Toxicol 99: 256–262.

Pawlowski, S. R. van Aerle, C.R. Tyler and T. Braunbeck. 2004. Effects of 17a-ethinylestradiol ina fathead minnow (*Pimephales promelas*) gonadal recrudescence assay. Ecotoxicol Environ Safety 57: 330-345.

Pohl, H. and H.G. Abadin. 1995. Utilizing uncertainty factors in minimal risk levels derivation. Regul Toxicol Pharmacol 22: 180-188.

Raimondo, S. and C.L. McKenney. 2006. From organisms to populations: Modeling aquatic toxicity data across two levels of biological organization. Environ Toxicol Chem 25(2): 589-596.

Raimondo, S., B.J. Montague and M.G. Barron. 2007. Determinants of variability in acute to chronic toxicity ratio for aquatic invertebrates and fish. Environ Toxicol Chem 26(9): 2019-2023.

Raimondo, S., C.R. Jackson and M.G. Barron. 2010. Influence of taxonomic relatedness and chemical mode of action in acute interspecies estimation models for aquatic species. Environ Sci Technol 44: 7711-7716.

Richards, S.M., C.J. Wilson, D.J. Johnson, D.M. Castle, M. Lam, S.A. Mabury, P.K. Sibley and K.R. Solomon. 2004. Effects of pharmaceutical mixtures in aquatic microcosms. Environ Toxicol Chem 23(4): 1035-1042.

Sanderson, H., D.J. Johnson, C.J. Wilson, R.A. Brain and K.R. Solomon. 2003. Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity in fish, daphnids and algae by ECOSAR screening. Toxicol Let 144: 383-395.

SCBT (Santa Cruz Biotechnology). 2017. On-line chemical brochure. Web page: https://www.scbt.com/scbt/product/citalopram-hydrobromide-59729-32-7. Accessed 05-24-17.

Schreurs, R.H.M.M., J. Legler, E. Artola-Garicano, T.L. Sinnige, P.H. Lanser, W. Seinen and B. Van Der Burg. 2004. In vitro and in vivo antiestrogenic effects of polycyclic musks in zebrafish. Environ Sci Technol 38(4): 997-1002.

Schubert, S., A. Peter, R. Burki, R. Schönenberger, M.J.-F. Suter, H. Segner and P. Burkhardt-Holm. 2008. Sensitivity of brown trout reproduction to long-term estrogenic exposure. Aquat Toxicol 90: 65–72.

Schultz, M.M., M.M. Painter, S.E. Bartell, A. Logue, E.T. Furlong, S.L. Werner and H.L. Schoenfuss. 2011. Selective uptake and biological consequences of environmentally relevant antidepressant pharmaceutical exposures on male fathead minnows. Aquat Toxicol 104: 38–47.

Schultz, M.M., S.E. Bartell and H.L. Schoenfuss. 2012. Effects of triclosan and triclocarban, two ubiquitous environmental contaminants, on anatomy, physiology, and behavior of the fathead minnow (Pimephales promelas). Arch Environ Contam Toxicol 63: 114–124.

Sharpe, R.L., D.L. MacLatchy, S.C. Courtenay and G.J. Van der Kraak. 2004. Effects of a model androgen (methyl testosterone) and a model anti-androgen (cyproterone acetate) on reproductive endocrine endpoints in a short-term adult mummichog (*Fundulus heteroclitus*) bioassay. Aquat Toxicol 67: 203-215.

Simon, T.W., Y. Zhu, M.L. Dourson and N.B. Beck. 2016. Bayesian methods for uncertainty factor application for derivation of reference values. Regul Toxicol Pharmacol 80: 9-24.

Slaninova, A., H. Modra, M. Hostovsky, E. Sisperova, J. Blahova, I. Matejova, M. Vicenova, M. Faldyna, L. Zelnickova, F. Tichy and Z. Svobodova. 2014. Effects of subchronic exposure to N,N-diethyl-m-toluimide on selected biomarkers in common carp (*Cyprinus carpio L.).* BioMed Res Internat Volume 2014, Article ID 828515. Hindawi Publishing Corp. 8pp.

Slooff, W., J.A.M. van Oers and D. De Zwart. 1986. Margins of uncertainty in ecotoxicological hazard assessment. Environ Toxicol Chem 5: 841-852.

Smith, S.B. and T. Muir. 1998. Investigations of endocrine disruption in aquatic systems associated with the National Water Quality Assessment (NAWQA) Program. USGS Fact Sheet FS-081-98.

Snow, D.D., S.L. Bartelt-Hunt, S. Devivo, S. Saunders and D.A. Cassada. 2009. Detection, occurrence, and fate of emerging contaminants in agricultural environments. Faculty Publications from The Water Center. Paper 9. http://digitalcommons.unl.edu/watercenterpubs/9

Snyder, E.M., S.A. Snyder, J.P. Geisy, S.A. Blonde, G.A. Hurlburt, S.L. Summer, R.R. Mitchell and D.M Bush. 2000. SCRAM: A scoring and ranking system for persistent, bioaccumulative, and toxic substances for the North American Great Lakes. Environ Sci Pollut Res 7(1): 51-51.

Sohoni, P., C.R. Tyler, K. Hurd, J. Caunter, M. Hetheridge, T. Williams, C. Woods, M. Evans, R. Toy, M. Gargas and J.P. Sumpter. 2001. Reproductive effects of long-term exposure to bisphenol a in the fathead minnow (*Pimephales promelas*). Environ Sci Technol 35: 2917-2925.

Springborn Bionomics Inc. 1984. Acute toxicity of tributoxyethyl phosphate to fathead minnow with attachments, cover sheets and letter dated 121890. Submitted by Monsanto Co. to USEPA under Section 8D of TSCA; received by USEPA on 122690. EPA Doc. ID: 86-910000303. TSCATS database Microfiche No. OTS0528533.

Spromberg, J.A. and J.P. Meador. 2005. Relating results of chronic toxicity responses to population-level effects: Modeling effects on wild chinook salmon populations. Integr Environ Assessm Manage 1(1): 9-21.

Stanko, J.P. and R.A. Angus. 2007. In vivo assessment of the capacity of androstenedione to masculinize female mosquitofish (*Gambusia affinis*) exposed through dietary and static renewal methods. Environ Toxicol Chem 26(5): 920-926.

Staples, C.A., A.T. Hall, U. Friederich, N. Caspers and G.M. Klecka. 2011. Early life-stage and multi generation toxicity study with Bisphenol A and fathead minnows (Pimephales promelas). Ecotoxicol Environ Safety 74: 1548–1557.

Stevenson, L.M., A.C. Brown, T.M. Montgomery and E.D. Clotfelter. 2011. Reproductive consequences of exposure to waterborne phytoestrogens in male fighting fish *Betta splendens*. Arch Environ Contam Toxicol 60: 501–510.

Styrishave, B., B. Halling-Sørensen and F. Ingerslev. 2011. Environmental risk assessment of three selective serotonin reuptake inhibitors in the aquatic environment: A case study including a cocktail scenario. Environ Toxicol Chem 30(1): 254-261.

Sun, L., J. Zha, P.A. Spear and Z. Wang. 2007. Toxicity of the aromatase inhibitor letrozole to Japanese medaka (*Oryzias latipes*) eggs, larvae and breeding adults. Compar Biochem Physiol Part C 145: 533-541.

Sun, L., J. Zha and Z. Wang. 2009. Effects of binary mixtures of estrogen and antiestrogens on Japanese medaka (Oryzias latipes). Aquat Toxicol 93: 83–89.

Sun, L., X. Lin, R. Jin, T. Peng, Z. Peng and Z. Fu. 2014. Toxic effects of Bisphenol A on early life stages of Japanese medaka (*Oryzias latipes*). Bull Environ Contam Toxicol 93: 222–227.

Suter, G. 1993. Ecological Risk Assessment. Lewis Publishers, Chelsea, MI. 538 pp.

Suter, G.W., II. 1996. Toxicological benchmarks for screening contaminants of potential concern for effects on freshwater biota. Environ Toxicol Chem 15(7): 1232-1241.

Thomas, L.M., Z.G. Jorgenson, M.E. Brigham, S.J. Choy, J.N. Moore, J.A. Banda, D.J. Gefell, T.A. Minarek and H.L. Schoenfuss. 2017. Contaminants of emerging concern in tributaries to the Laurentian Great Lakes: II. Biological consequences of exposure. PLoS ONE 12(9): e0184725. https://doi.org/10.1371/journal.pone.0184725.

Thomas, M.A. and R.D. Klaper. 2012. Psychoactive pharmaceuticals induce fish gene expression profiles associated with human idiopathic autism. PloS One 7(6): 1-8. Doc No. e32917.

Thomas, M.A., P.P. Joshi and R.D. Klaper. 2012. Gene-class analysis of expression patterns induced by psychoactive pharmaceutical exposure in fathead minnow (*Pimephales promelas*) indicates induction of neuronal systems. Compar Biochem Physiol Part C 155: 109-120.

Thorpe, K.L., R.I. Cummings, T.H. Hutchinson, M. Scholze, G. Brighty, J.P. Sumpter and C.R. Tyler. 2003. Relative potencies and combination effects of steroidal estrogens in fish. Environ Sci Technol 37: 1142-1149.

Thorpe, K.L., R. Benstead, T.H. Hutchinson and C.R. Tyler. 2007. Associations between altered vitellogenin concentrations and adverse health effects in fathead minnow (*Pimephales promelas*). Aquat Toxicol 85: 176-183.

Thorpe, K.L., R. Benstead, P. Eccles, G. Maack, T. Williams and C.R. Tyler. 2008. A practicable laboratory flow-through exposure system for assessing the health effects of effluents in fish. Aquat Toxicol 88: 164–172.

Thorpe, K.L., M.L.M. Pereira, H. Schiffer, P. Burkhardt-Holm, K. Weber and J.R. Wheeler. 2011. Mode of sexual differentiation and its influence on the relative sensitivity of the fathead minnow and zebrafish in the fish sexual development test. Aquat Toxicol 105: 412–420.

Tremblay, L. and G. Van Der Kraak. 1999. Comparison between the effects of the phytosterol B-sitosterol and pulp and paper mill effluents on sexually immature rainbow trout. Environ Toxicol Chem 18(2): 329–336.

UNEP (United Nations Environment Programme). 2010. Clearing the waters: A focus on water quality solutions. 88 pp. Prepared by: Pacific Institute, Oakland, CA. Prepared for: UNEP, Division of Environmental Policy Implementation. http://www.unep.org/PDF/Clearing_the_Waters.pdf

UNEP. 2014. The Chemicals in Products Project. Web page: http://www.unep.org/chemicalsandwaste/UNEPsWork/ChemicalsinProductsproject/tabid/56141/Default.aspx. Accessed 07-02-2014.

USEPA (U.S. Environmental Protection Agency). 1985. Guidelines for deriving numerical national water quality criteria for the protection of aquatic organisms and their uses. Doc. No. PB85-227049. USEPA, ORD, Environmental Research Laboratories.

USEPA. 1989. Risk assessment guidance for Superfund - Volume I human health evaluation manual (Part A): Interim Final. EPA Doc. No. EPA/540/1-89/002. December, 1989.

USEPA. 1993a. Office of Water policy and technical guidance on interpretation and implementation of aquatic life metals criteria. Memo from: Martha G. Prothro, Acting Assistant Administrator for Water. Memo to: USEPA Water Management Division Directors, Environmental Services Division Directors, Regions I-X. Web availability: https://www3.epa.gov/npdes/pubs/owm0316.pdf

USEPA. 1993b. Reference Dose (RfD): Description and use in health risk assessments: Background document 1A. USEPA, Integrated Risk Information System (IRIS). March 15, 1993. Web page accessed on 12/12/2016: https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments#1.3.2

USEPA. 1995. Final water quality guidance for the Great Lakes system. Federal Register 60(56): 15366-15452.

USEPA. 1996a. Ecotox Thresholds. ECO Update. USEPA Office of Emergency and Remedial Response. Intermittent Bulletin 3(2): 1-12. EPA Doc. No. EPA 540/F-95/038.

USEPA. 1996b. Ecological Effects Test Guidelines: OPPTS 850.1075 Fish Acute Toxicity Test, Freshwater and Marine. USEPA Office of Prevention, Pesticides and Toxic Substances (OPPTS). EPA Doc. No. EPA 712–C–96–118. April, 1996.

USEPA. 1996c. Ecological Effects Test Guidelines: OPPTS 850.1400 Fish Early-Life Stage Toxicity Test. USEPA Office of Prevention, Pesticides and Toxic Substances (OPPTS). EPA Doc. No. EPA 712–C–96–121. April, 1996.

USEPA. 1996d. Ecological Effects Test Guidelines: OPPTS 850.1500 Fish life cycle toxicity. USEPA Office of Prevention, Pesticides and Toxic Substances (OPPTS). EPA Doc. No. EPA EPA712–C–96–122. April, 1996

USEPA. 1997. Ecological risk assessment guidance for Superfund: Process for designing and conducting ecological risk assessments. Interim Final. EPA Doc. No. EPA-540-R-97-006. USEPA, OSWER. June, 1997. http://www.epa.gov/oswer/riskassessment/ecorisk/ecorisk.htm

USEPA. 1999. User Guide: Acute to chronic estimation. USEPA, ORD. EPA Doc. No. EPA/600/R-98/152. January, 1999.

USEPA. 2001. Eco Update: The role of screening-level risk assessments and refining contaminants of concern in baseline ecological risk assessments. USEPA, OSWER. EPA Doc. No. EPA-540-F-01-014. June, 2001.

USEPA. 2004. Overview of the ecological risk assessment process in the Office of Pesticide Programs, U.S. Environmental Protection Agency: Endangered and Threatened Species Effects Determinations. USEPA, OPPTS, OPP. January, 2004.

USEPA. 2005. Aquatic life ambient water quality criterion – nonylphenol. Final. USEPA, Office of Water. EPA Doc. No. EPA-822-R-05-005. December, 2005.

USEPA. 2007a. Method 1698: Steroids and hormones in water, soil, sediment, and biosolids by HPLC/MS/MS. EPA Doc. No. EPA-821-R-08-003. December, 2007.

USEPA. 2007b. Method 1694: Pharmaceuticals and personal care products in water, soil, sediment, and biosolids by HPLC/MS/MS. USEPA, Office of Water. EPA Doc. No. EPA-821-R-08-002. December, 2007.

USEPA. 2008a. White Paper: Aquatic life criteria for contaminants of emerging concern. Part 1. General challenges and recommendations. Prepared by OW/ORD Emerging Contaminants Workgroup. Draft Document. June 3, 2008.

USEPA. 2008b. SAB Advisory on Aquatic Life Water Quality Criteria for Contaminants of Emerging Concern. EPA Doc. No. EPA-SAB-09-007. Memo from: Deborah Swackhamer (Chair, Science Advisory Board) and Judith L. Meyer (Chair, Ecological Processes and Effects Committee). Memo to: Steven L. Johnson (Administrator, USEPA). Memo Dated: December 18, 2008.

USEPA. 2009a. Summary Report: Risk assessment forum technical workshop on population-level ecological risk assessment. USEPA Office of the Science Advisor, Risk Assessment Forum. EPA Doc. No. EPA/100/R-09/006. October 2009.

USEPA. 2009b. Summary Report: Risk assessment forum technical workshop on population-level ecological risk assessment. Supplementary Material: Workshop Presentations. USEPA Office of the Science Advisor, Risk Assessment Forum. EPA Doc. No. EPA/100/R-09/006. October 2009.

USEPA. 2015a. List of Lists: Consolidated List of Chemicals Subject to the Emergency Planning and Community Right- To-Know Act (EPCRA), Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and Section 112(r) of the Clean Air Act. USEPA, OSWER. EPA Doc. No. EPA 550-B-15-001. March, 2015. Web page accessed on 11/23/2016: https://www.epa.gov/epcra/epcracerclacaa-ss112r-consolidated-list-lists-march-2015-version

USEPA. 2015b. Region 4 Ecological Risk Assessment Supplemental Guidance Interim Draft. USEPA, EPA Region 4, Superfund Division, Scientific Support Section. Web page accessed on 12/12/2016: https://www.epa.gov/risk/region-4-ecological-risk-assessment-supplemental-guidance

USEPA. 2016a. Priority Pollutant List. Web page accessed on 11/23/2016: https://www.epa.gov/eg/toxic-and-priority-pollutants-under-clean-water-act

USEPA. 2016b. National recommended water quality criteria - Aquatic life criteria table. Web page accessed on 09/27/2016: https://www.epa.gov/wqc/aquatic-life-ambient-water-quality-criteria

USEPA. 2016c. ECOTOX (Version 4) on-line database. USEPA, Mid-Continent Division, Duluth, MN. Web page accessed on 09/21/2016: https://cfpub.epa.gov/ecotox/

USEPA. 2016d. Web-based interspecies Correlation Estimation (Web-ICE) for Acute Toxicity: User Manual. Version 3.3. Prepared by USEPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory Gulf Ecology Division. EPA Doc. No. EPA/600/R-15/192. June, 2016.

U.S. Geological Survey (USGS). 2006. Determination of wastewater compounds in whole water by continuous liquid-liquid extraction and capillary-column gas chromatography/mass spectrometry. U.S. Geological Survey Techniques and Methods, Book 5, Chap. B4, 30pp.

USGS. 2012. Determination of steroid hormones and related compounds in filtered and unfiltered water by solid-phase extraction, derivatization, and gas chromatography with tandem mass spectrometry. U.S. Geological Survey Techniques and Methods, Book 5, Chap. B9, 118pp.

USGS. 2014. Determination of Human-Use Pharmaceuticals in filtered water by direct aqueous injection-high performance liquid chromatography/tandem mass spectrometry. U.S. Geological Survey Techniques and Methods, Book 5, Chap. B10, 49pp.

Van den Belt, K., P. Berckmans, C. Vangenechten, R. Verheyen and H. Witters. 2004. Comparative study on the in vitro/in vivo estrogenic potencies of 17ß-estradiol, estrone, 17α-ethynylestradiol and nonylphenol. Aquat Toxicol 66: 183–195.

Van der Hoeven, N., F. Noppert and A. Leopold. 1997. How to measure no effect. Part I: Towards a new measure of chronic toxicity in ecotoxicology. Introduction and workshop results. Environmetrics 8: 241-248.

von der Ohe, P.C., V. Dulio, J. Slobodnik, E. DeDeckere, R. Kuhne, R.U. Ebert, A. Ginebreda, A. DeCooman, G. Schuurmann and W. Brack. 2011. A new risk assessment approach for the prioritization of 500 classical and emerging organic microcontaminants as potential river basin specific pollutants under the European Water Framework Directive. Sci Total Environ 409: 2064-2077.

Waring, C.P. and A. Moore. 2004. The effect of atrazine on Atlantic salmon (Salmo salar) smolts in fresh water and after sea water transfer. Aquat Toxicol 66: 93-104.

Warne, M.S.J. and R. van Dam. 2008. NOEC and LOEC data should no longer be generated or used. Australian J Ecotoxicol 14: 1-5.

Wheeler, J.R., S.K. Maynard and M. Crane. 2014. An evaluation of fish early life stage tests for predicting reproductive and longer-term toxicity from plant protection product active substances. Environ Toxicol Chem 33(8): 1874-1878.

Wilde, F.D., L.J. Britton, C.V. Miller D.W. Kolpin. 2000. Effects of animal feeding operations on water resources and the environment. Proceedings of the Technical Meeting, Fort Collins, Colorado, August 30-September 1, 1999. USGS Open-File Report 00-204.

Williams, E.S., J.P. Berninger and B.W. Brooks. 2015. Application of chemical toxicity distributions to ecotoxicology data requirements under REACH. Environ Toxicol Chem 30(8): 1943-1954.

Wright-Walters, M., C. Volz, E. Talbott and D. Davis. 2011. An updated weight of evidence approach to the aquatic hazard assessment of Bisphenol A and the derivation a new predicted no effect concentration (PNEC) using a non-parametric methodology. Sci Total Environ 409: 676-685.

Wu, M., H. Xu, Y. Shen, W. Qiu and M. Yang. 2011. Oxidative stress in zebrafish embryos induced by short-term exposure to bisphenol A, nonylphenol, and their mixture. Environ Toxicol Chem 30(10): 2335–2341.

Wüthrich, V. 1996. HHCB: 21-day prolonged toxicity study in the bluegill sunfish under flow-through conditions. Report to RIFM, RCC Umweltchemie AG Project 380711. As cited in Balk and Ford 1999.

Xu, H., M. Yang, W. Qiu, C. Pan and M. Wu. 2013. The impact of endocrine-disrupting chemicals on oxidative stress and innate immune response in zebrafish embryos. Environ Toxicol Chem 32(8): 1793–1799.

Yu, L., J.C.W. Lam, Y. Guo, R.S.S. Wu,P.K.S. Lam and B. Zhou. 2011. Parental transfer of polybrominated diphenyl ethers (PBDEs) and thyroid endocrine disruption in zebrafish. Environ Sci Technol 45: 10652–10659.

Zeeman, M. 1995. EPA's framework for ecological effects assessment. In Screening and Testing Chemicals in Commerce – Background Paper. Congress of the US, Office of Technology Assessment. Doc. No. OTA-BP-ENV-166. September, 1995.

Zenobio, J.E., B.C. Sanchez, L.C. Archuleta and M.S. Sepulveda. 2014. Effects of triclocarban, n,n-diethyl-meta-toluamide, and a mixture of pharmaceuticals and personal care products on fathead minnows (*Pimephales promelas*). Environ Toxicol Chem 33(4): 910–919.

Zhao, J., G. Ying, Y. Liu, F. Chen, J. Yang, L. Wang, X Yang, J. Stauber and M. Warne. 2010. Occurrence and a screening-level risk assessment of human pharmaceuticals in the Pearl River system, South China. Environ Toxicol Chem 29(6): 1377–1384.

ATTACHMENT 1-1.

List of CECs commonly detected in unfiltered surface water during 2010-2012 at sampling sites in the Great Lakes Basin.

Androstene-3,17-dione, 4-
* Androsterone, cis-
* Benzophenone
Bisphenol A
Carbamazepine
* Chloroxylenol
Citalopram
* Coprostanol, 3-beta-
* Cotinine
DEET
* Diltiazem
Diphenhydramine
Estrone
Hexahydrohexamethylcyclopentabenzopyran (HHCB)
Ibuprofen
* Iminostilbene
Lidocaine
Metolachlor
Phenytoin
Sitosterol, beta-
* Tramadol
Triclosan
* Triethyl citrate
Tris(2-butoxyethyl)phosphate (TBEP)
Venlafaxine

Shading = CECs for which published ecotoxicity information was sufficient to derive a pair of SVs

\# = CECs for which limited fish ecotoxicity information was located, which was insufficient to derive the pair of SVs

* = CECs for which no published lab ecotoxicity studies in fish were located in literature searches

ATTACHMENT 2-1.

Guide to Effect Categories, Adverse Effect Endpoints,
and Population-relevance in the CEC Fish Ecotoxicity Database

The underlined headers below, in Sections 2-1.1 and 2-1.2, designate 13 Effect Categories that may be included in the CFED. No other effect categories have been entered into the database. These are conventional terms commonly used by agencies involved in human health and/or ecological risk assessment of chemical impacts (e.g., ATSDR (no date), USEPA 1997) and ecotoxicological research in fish. For each Effect Category, study design features, example key words, and usage guidelines are described. This guide is intended to:

- assist data entry personnel with consistently assigning study results to different Effect Categories in the CFED, and with consistently assigning adverse and population-relevant designations to specific effect endpoints
- assist database users with understanding database contents and locating information of interest.

All effect endpoints (both adverse and other) that are listed below were used to develop UF values, while SVs were derived from only adverse effect endpoints.

Relative adversity of effect endpoints is a topic of interest in the ecotoxicity literature (e.g., Lewis et al. 2002). Our approach likewise distinguishes "adverse" from other effects. Effects not designated as adverse include the following types of endpoints:

- bioindicators of exposure (e.g., elevated vitellogenin in male fish after exposure to estrogenic chemicals),
- adaptive effects (e.g., hepatomegaly),
- effects associated with exposure to xenobiotics generally (e.g., liver enzyme induction), or
- precursor effects in an adverse outcome pathway that have not yet been quantitatively linked to adverse apical effects (e.g., altered mRNA expression)

We designated population-relevance of effect endpoints based on scientific judgement, as informed by the literature. USEPA (1997) guidance for developing screening ecotoxicity values indicates a clear preference for effect endpoints "that can impact populations", including "adverse effects on development, reproduction, and survivorship." For the purpose of deriving population-relevant SVs, we define population-relevant effect endpoints as those that directly relate to survival, propagation, or growth, where laboratory exposure-response information could be readily incorporated into a quantitative, mechanistic population dynamics model (Figure 2-2).

The integration of population modeling with laboratory-derived ecotoxicity data to assess population-level impacts of chemical exposures in ecological receptors has had a consistent representation in the literature for decades (e.g., Baldwin et al. 2009, Barnthouse et al. 1987, Brown et al. 2003, Forbes et al. 2011, Forbes et al. 2016, Pastorok et al. 2003, Raimondo and McKenney 2006, Spromberg and Meador 2005, USEPA 2009a, USEPA 2009b), and has been recommended by the National Academy of Sciences for prospective EHAs evaluating the potential for pesticide impacts to threatened and endangered species (NAS 2013). Survival and reproductive effect endpoints are of obvious relevance to population modeling. But, there also has been increasing attention in the ecological risk assessment literature to incorporating adverse growth and certain developmental and behavioral endpoints to interpret the potential for chemical impacts to fish populations (e.g., Hamilton et al. 2016, Hazlerigg et al. 2014, Marty et al 2016). Our designations of population-relevance indicated below in Section 2-1.1 were based on scientific judgment that reflects these trends and patterns in the literature.

No fish ecotoxicity effects in the database were reported as population- or community-level endpoints[22] , *per se*, and none were located in the fish ecotoxicity literature for the CECs considered in this document. We recognize that the individual organism is the unit of observation in nearly all fish ecotoxicity assays, so all effect endpoints are necessarily suborganism- or organism-level endpoints.

It may be argued legitimately that all adverse effects are ultimately related to the survival and propagation of populations by influencing stress levels and energetics in the individuals comprising the populations. However, not all adverse effect endpoints as reported in ecotoxicity studies may be converted readily and quantitatively into effects on survival, propagation, or growth. Low levels of stress or energy expenditure related to certain types of adverse effects from CEC exposures, such as shifts in hematological parameters or plasma

[22]Examples of endpoints at the population and community levels of ecological organization:
- Population - absolute or relative abundance, intrinsic or finite rate of increase, sex ratio, age distribution, life table structure, etc.
- Community - trophic structure, food web complexity, richness or diversity at various taxonomic levels, etc.

chemistry, micronucleus formation, discoloration of liver, or alterations in blood antibody concentrations may, in themselves, likely have limited direct impacts on populations of fish. However, other effect endpoints designated as "population-relevant" are more clearly, directly, and quantifiably related to survival and propagation of populations as reported in the primary literature. Examples of these include mortality, reduced egg hatchability, reduced sperm viability, reduced predator avoidance, increased embryonic deformations or functional deficiencies, reduced larval growth, and increased susceptibility to lethal pathogens.

In the CEC SV derivation process, Population-relevant effect endpoints are associated with the following Effect Categories: Developmental, Growth, Survival/Mortality, Reproductive, and Behavioral. In contrast, derivation of comprehensive SVs utilized all CEC-specific NOAECs and LOAECs in all Effect Categories.

2-1.1 Effect Categories that Include Population-Relevant Endpoints

Behavioral

Description: These endpoints are related to physical movement or orientation in response to chemical (and possibly additional) stimuli. Included are endpoints related to:

- activity patterns, responses to stimuli, or behavioral clinical signs of toxicity in fish exposed individually, and
- altered interactions (e.g., mating displays, resource competition, aggression, or predator-prey interactions) between fish exposed in groups or between an exposed fish and an unexposed challenge organism or simulated organism.

Exposure: Any life stage; any exposure duration

Life Stages Evaluated: Effects may be evaluated in any life stage.

Population-Relevant Adverse Endpoints: Based on scientific judgement on a case-by-case basis, these include behavioral endpoints related to:

- survival (e.g., startle response time, swimming speed, predator avoidance, or feeding rate), or
- reproduction (e.g., nest defense or spawning behaviors).

Other Adverse Endpoints: Endpoints not related to survival or reproduction behaviors that could be integrated into a quantitative, mechanistic population model – e.g., righting reflex or light-dark preferences.

Other Endpoints: None; all behavioral endpoints were considered adverse.

Exclusions: None; all behavioral endpoints are included in this Effect Category.

Developmental

Description: These effects occur post-fertilization in the exposed generation, or in subsequent generations.

Exposure: Exposure may occur in any life stage and any duration, but at least some of the exposure must occur in early life stages within the same generation being evaluated, and/or any life stage(s) in generation(s) prior to the generation being evaluated within a multigenerational study.

Life Stages Evaluated: For the most part, effects that are observed in early life stages (embryo, larva, fry) are reported under the Developmental Effect Category. Abnormalities in immature and adult fish may also be reported, but only if exposure had occurred during a developmental life stage of the same generation, or in a previous generation. Life cycle tests and early life stage tests typically include developmental endpoints.

Population-Relevant Adverse Endpoints: sex ratio, early life stage growth and survival; timing, rate, success of hatch; anatomical deformations or malformations[23] .

Other Adverse Endpoints: occurrence of intersex[24], metabolic, hormonal, genetic, gross or histological, immunological, circulatory/blood, neurological, and/or physiological abnormalities in early life stages, or in juvenile or adult life stages if exposure had occurred as specified above.

Other Endpoints: Enzyme inhibition, induction or activity, mRNA expression of genes.

Exclusions: Behavioral and Cancer endpoints observed during early life stages are included in those Effect Categories, not in Developmental.

[23] Severe anatomical deformations and malformations have been observed to directly impact embryo or larval survival under laboratory conditions. Developmental toxicity assays do not typically track survival of malformed versus unaffected individuals through adulthood. Even if severe malformations (such as spinal curvature) were not observed to affect early life stage survival under laboratory conditions, it is reasonable to assume that such malformations would contribute to high mortality rates during later life stages in wild populations. Less severe deformities that are not directly fatal may indirectly adversely impact survival and reproduction in fish populations in real aquatic systems by affecting ability to capture prey and/or avoid predators, impact mating performance, or reduce resource competitiveness. Other deformations, such as elongated sword in a swordtail fish, have unknown but suspected negligible relevance to fish survival and reproduction. For these reasons, developmental endpoints were individually assessed using professional judgment as to their utility to quantitative, mechanistic modelling of population sustainability.

Growth
Description: Effects related to body size.

Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; any exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish, only.

Population-Relevant Adverse Endpoints: changes in whole body size, such as body weight, various length metrics, girth, and condition index (weight/length).

Other Adverse Endpoints: changes in morphological characteristics with unknown adverse consequences

Other Endpoints: changes in specialized morphological characteristics, such as, decrease in sword length in swordtail fish

Exclusions: Growth endpoints observed in early life stages should be included under Developmental.

Mortality/Survival
Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish, only.

Population-Relevant Adverse Endpoints: Reported results are sufficient to identify a LOAEC and/or NOAEC for mortality, which is the only endpoint included under this Effect Category. Reported LCxx values are not included.

Other Adverse Endpoints: None

Other Endpoints: None

Exclusions: Early life stage mortality/survival data are included only under Developmental. Behavioral endpoints related to mortality, such as predator avoidance, are included under the Behavioral Effects Category.

Reproductive
Description: Endpoints are events and effects related to, and influencing the capacity for, successful procreation - up to and including fertilization.

Exposure: Sexually immature (fingerling, juvenile, subadult) or mature (adult) fish, or direct pre-fertilization exposure of gametes; any exposure duration

Life Stages Evaluated: Effects evaluated in parental (adult) fish, gametes, or embryos, only.

Population-Relevant Adverse Endpoints: functional changes in reproductive organs of exposed adults; gametogenesis; production, survival, mobility, size, and viability of gametes; timing, frequency, and success of spawning; fertilization success, GSI.

Other Adverse Endpoints: reproductive effect endpoints that are not readily quantifiable with respect to reduction in the capacity for procreation, such as: external structural change in reproductive organs of exposed adults; reproductive hormone levels; gross pathology or histopathology of reproductive organs; external secondary sex characteristics.

Other Endpoints: mRNA expression of hypothalamus-pituitary-gonad axis genes; biomarkers of exposure to estrogenic or androgenic contaminants (e.g., vitellogenin as biomarker for exposure to an estrogenic substance).

Exclusions: Behavioral endpoints related to reproduction are included under the Behavioral Effects Category; changes in reproductive organs in early life stages are reported under the Developmental Effects Category

2-1.2 Other Effect Categories[25]

Circulatory/Blood Constituents
Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stage effects should only be included under the Developmental Effect Category]

[24] Intersex is a commonly measured metric of CEC effects, particularly when exposure to estrogenic substances is suspected. While intersex is considered an adverse effect to an individual fish, the mere presence of oocytes in fish testes does not preclude the viability or sufficient quantity of that fish's spermatocytes such that overall reproduction in the population is not impacted. Harris et al. (2011) found that even severely affected males do sire offspring. While it is possible that the occurrence of intersex is indeed indicative of significant reproductive impacts, no peer-reviewed laboratory study quantifying a functional relationship between the occurrence of intersex and reduction in fish reproductive success was located. Harris et al. (2011) found that proportion of offspring sired per male fish was negatively related to intersex index in a severely polluted river. However, it is not clear whether intersex is the driving variable, or simply correlated with the principal effect. That is, it is not clear in the Harris et al. (2011) in situ study whether reduction in reproductive performance was due to alterations in classic reproductive endpoints or to disruption of reproductive behavior, or to some other unidentified effect from exposure to estrogenic chemicals, or other chemicals. Hence, for the purposes of this document and until lab studies provide further clarity, intersex is tentatively designated a non-population-relevant adverse Reproductive endpoint.

Description: Endpoints include physiological, functional, or anatomical pathology of heart or blood vessels; blood cell formation, bone marrow, lymph nodes, spleen, thymus; hematological parameters, blood or plasma chemistry; and heart enzymes in blood.

Endocrine/Hormone

Exposure: sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stage effects should only be included under the Developmental Effect Category]

Description: Endpoints include: measured concentrations of endogenous steroid and non-steroid, endocrine and neuroendocrine hormones, hormone precursors, or hormone metabolites in various tissues; evaluations of gross pathology or histopathology in organs and tissues related to the endocrine and neuroendocrine systems (e.g., hypothalamus, pituitary, thyroid, pancreas, adrenal gland, or pineal gland).

Reproductive hormone levels and effects in reproductive organs are not included here; they are included in the Reproductive Effects Category

Genotoxicity

Exposure: sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stage effects should only be included under the Developmental Effect Category]

Description: Endpoints include: RNA/DNA ratio; DNA or RNA fragmentation or other damage; nucleic acid synthesis; mutations such as nucleotide substitution; chromosomal damage or aberrations; incomplete or otherwise abnormal cell division, mitosis, or meiosis; micronucleus formation; cell nucleus abnormalities; abnormal DNA synthesis or sequences.

Gross Pathology

Exposure: sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stage effects should only be included under the Developmental Effect Category]

Description: Endpoints include morphology and external features of the whole fish and organs, including: overall coloration, spotting, and macroscopic lesions; organ size as absolute organ weights or relative weight (e.g., HSI); enzymes in blood indicative of specific organ damage. Nodules, other non-cancer growths, rough surfaces, and other surficial tissue anomalies are included here.

Exclusions:

- Pre-cancerous and cancerous lesions should only be included in the Cancer Effect Category,
- Pathology endpoints for certain organs/ tissues that are principally related to other Effect Categories should not be included here, such as Reproductive, Circulatory, Endocrine, or Neurological
- Pathologies in early life stages should be reported under Developmental

Histopathology

Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stages are included under Developmental Effect Category]

Description: Endpoints evaluated internally in organs and tissues include microscopic lesions, cellular changes, ultrastructural (subcellular, organelle) changes, etc.

[Early Life Stages are included under Developmental Effect Category, and hematology, gametogenesis stages, and histopathology in reproductive organs are called out in other Effect Categories]

[25] The CEC Fish Ecotoxicity Database (CFED) generated in this study included principally subchronic or chronic exposure duration data. Future updates of the database and CEC SVs may include acute an Acute Toxicity Effect Category to record LCxx or ECx toxicity data if an empirical exposure duration uncertainty factor is eventually developed. No laboratory assays for the 14 subject CECs in this document reported cancer endpoints. Database updates may include a Cancer Effect Category if cancer endpoints are reported in future lab studies in freshwater fish.

Immunological
Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stages are included under Developmental Effect Category]

Description: Endpoints are related to immune system function, and may include inflammatory or autoimmune responses, pathogen susceptibility, or levels of circulating immunoglobulins, lymphocytes, macrophages, neutrophils and eosinophils, antibodies, antibacterial peptides, interferons, cytokines, lytic enzymes (e.g., lysozyme), phagocytes, etc.

Neurological
Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stages are included under Developmental Effect Category]

Description: Effects are related to neuroanatomy or neurophysiology. Endpoints may include neurotransmitter activity or gene expression, receptor abundance, activation potential, central nervous system (CNS), peripheral nervous system (PNS), locomotor, sensory, mechanosensory, brain, spinal cord, cranial nerve, axon, dendrite, synapse, olfactory, ocular, etc.

Physiological/Metabolic
Exposure: Sexually immature (fingerling, juvenile) or mature (adult) fish; subchronic or chronic exposure duration

Life Stages Evaluated: Effects evaluated in exposed sexually immature (fingerling, juvenile) or mature (adult) fish.

[Early Life Stages are included under Developmental Effect Category]

Description: Wide variety of effects related to biochemical function, and maintenance of homeostasis (including osmoregulation). Endpoints include: respiration rate, ventilation rate, or oxygen consumption; stress indicators, oxidative stress, or antioxidant abundance or activity; enzyme synthesis, enzyme system induction (e.g., cytochrome P450), or specific enzyme activity in any tissue (except blood); food assimilation efficiency, energy metabolism (e.g., glycolysis); alterations of mRNA transcription or translation; xenobiotic metabolism rates/metabolites; environmental preferences or tolerances (e.g., thermal tolerance).

ATTACHMENT 3-1. Summary of Literature on Laboratory Chemical Mixture Toxicity Studies Concerning Emerging Contaminants in Fish

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Binary Mixture (synthetic estrogen, inorganic)	17a-ethinylestradiol (EE2), Total ammonia nitrogen (TAN)	***Mortality; Reproductive:*** Plasma and liver Vitellogenin, eggs produced, eggs spawned	Mortality significantly higher (28.6%) than control (4.8%).	Mortality not significantly different from control for either treatment group. No significant differences in vitellogenin, fertilization rate, or egg production /female/day among all groups (including mixture and control)	Fathead Minnow	21 days	Water	Single CEC exposures EE2 only: 0.25 ng/L TAN: 2.26 mg/L (0.034 mg/L NH3), plus control Mixture exposure: Same concentrations		Armstrong et al. 2015
Flame Retardants	2,3,4,5-tetrabromo-ethylhexylbenzoate (TBB), and 2,3,4,5-tetrabromo-bis(2-ethylhexyl) phthalate (TBPH)	***Genotoxicity:*** DNA damage; ***Mortality***	reversible DNA damage; no mortality	Not reported	Fathead Minnow (M only)	56 days	Diet	Control, TBB: 1658 ug/g TBPH: 745 ug/g	Firemaster 550	Bearr et al. 2010
Flame Retardants	2,3,4,5-tetrabromo-ethylhexylbenzoate (TBB), and 2,3,4,5-tetrabromo-bis(2-ethylhexyl) phthalate (TBPH)	***Genotoxicity:*** DNA damage; ***Mortality***	reversible DNA damage; no mortality	Not reported	Fathead Minnow (M only)	56 days	Diet	Control, TBB: 2087 ug/g TBPH: 907 ug/g	Firemaster BZ-54	Bearr et al. 2010
Estrogenic Chemicals (hormones, phenols, plasticizer)	17B-estradiol (E2), 17a-ethinylestradiol (EE2), Nonylphenol (NP), Octylphenol (OP), Bisphenol A (BPA)	***Reproductive:*** vitellogenin induction	vitellogenin induced; concentrations almost exactly additive	Vitellogenin induced; exposure-response curves, EC50s, equipotent concentrations determined	Fathead Minnow (M & F)	14 days	Water	6 exposure levels plus control EE2: 0.03-1.0 ng/L; E2: <0.8-28 ng/L; NP: 0.4-5.5 ug/L OP: 1.5-32 ug/L; BPA: 4.1-110 ug/L	Experiment 1: range-finding study; fixed ratio dilution series	Brian et al. 2005

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (hormones, phenols, plasticizer)	17B-estradiol (E2), 17a-ethinylestradiol (EE2), Nonylphenol (NP), Octylphenol (OP), Bisphenol A (BPA)	***Reproductive:*** vitellogenin induction	vitellogenin induced; equipotent exposure concentrations additive; concluded similar mode of action	At 1/5 EC50, no vitellogenin inductions	Fathead Minnow (M & F))	14 days	Water	6 exposure levels plus control, fixed ratio design EE2: 0.13 ng/L; E2: 6 ng/L; NP: 1.8 ug/L OP: 9.4 ug/L; BPA: 20 ug/L	Experiment 2: mixture additivity study	Brian et al. 2005
Plant Hormones	B-sitosterol (80%), B-sitostanol, Campesterol, Campestanol	***Reproductive:*** Plasma concentrations of vitellogenin, testosterone, 17B-estradiol, and 11-ketotestosterone; gonad histopathology	Vitellogenin induced in males	Not reported	Zebrafish (M&F)	21 days	Water	0, 10, 100 ug/L of the mixture	Mixture called Ultrasitosterol	Christianson -Heiska et al 2007
Plant Hormones	B-sitosterol (80%), B-sitostanol, Campesterol, Campestanol	***Reproductive:*** Plasma concentrations of vitellogenin, testosterone, 17B-estradiol, and 11-ketotestosterone; gonad histopathology	M: elevated serum T and 11-KT, accelerated spermatogenesis F: increased follicular atresia, incr follicular T production	Not reported	Zebrafish (M&F)	21 days	Water	0, 10, 100 ug/L of the mixture	Oxidized ultrasitosterol	Christianson -Heiska et al 2007
Estrogenic Chemicals (hormones, plasticizer)	17B-estradiol (E2), 17a-ethinylestradiol (EE2), Bisphenol A (BPA)	***Reproductive:*** vitellogenin induction	vitellogenin induced; equipotent exposure concentrations additive	Vitellogenin induced; exposure-response curves, EC50s, equipotent concentrations determined	Sea bass (juvenile; sexually undifferentiated)	14 days	Water	Solvent control Positive control E2: 10-1000 ng/L EE2: 10-2000 ng/L BPA: 10-1600 ug/L	Marine species; fixed ratio dilution series; mixture additivity study	Correia et al 2007

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals	Acetaminophen Carbamazepine Gemfibrozil Venlafaxine	***Growth;*** ***Reproductive:*** Egg production, embryo viability, gonad pathology, plasma estradiol and 11-ketotestosterone; ***Histopathology:*** gill, liver, kidney; ***Developmental:*** Embryo abnormalities, hatchability, and mortality	Reduced viable embryos per female; no developmental effects in embryos from exposed adults; in high exposure group, increased mortality and developmental abnormalities in embryos directly exposed	Not reported	Zebrafish (M&F adults; embryos)	Adults: 42 days Embryos from unexposed adults: 3 days	Water	0, 0.5, 10 ug/L of each CEC in the mixture for control, low, and high exposure groups		Galus et al. 2013a
WWTP effluent	Complex mixture	***Growth;*** ***Reproductive:*** Egg production, embryo viability, gonad pathology, plasma estradiol and 11-ketotestosterone; ***Histopathology:*** gill, liver, kidney; ***Developmental:*** Embryo abnormalities, hatchability, and mortality	Reduced viable embryos per female; reduced 11-KT in adult males; no developmental effects in embryos from exposed adults; in high exposure group, increased developmental abnormalities in embryos directly exposed	Not reported	Zebrafish (M&F adults; embryos)	Adults: 42 days Embryos from unexposed adults: 3 days	Water	0, 5%, 25% (0, 1:19, and 1:3 effluent to water dilutions) of WWTP effluent for control, low, and high exposure groups	WWTP from community of 430,000; secondary activated sludge treatment; 40% combined and 60% separated sewers	Galus et al. 2013b

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Complex Mixtures (Surfactant plus Estrogenic Chemicals: hormones, phenols, plasticizer)	Linear alkylbenzene sulfonate (LAS), 17B-estradiol (E2), 17a-ethinylestradiol (EE2), Nonylphenol (NP), Octylphenol (OP), Bisphenol A (BPA)	***Reproduction:*** Plasma Vitellogenin	Plasma vitellogenin was elevated over control after 2 weeks exposure to the *estrogenic mixture alone*, but not after 1 week exposure. However, 1-week plasma vitellogenin for most mixture+surfactant treatments appeared to be elevated above control. Addition of surfactant only at highest concentration (362 ug/L) elevated plasma vitellogenin above that seen after estrogenic mixture alone after 1 week exposure.	Not reported	Fathead minnow (adult male)	7 or 14 days	Water	Concentrations of estrogenic stock mixture components were at respective EC20s (actual concentrations provided by author via personal communication). Separate test mixtures were prepared from the estrogenic stock mixture, combined with LAS at the following mean measured concentrations (ug/L): LAS: 23, 40, 85, 115, 187, 362 PLUS solvent (DMF) negative control	Estrogenic mixture components at EC20s, computed from conc-response curves determined by Brian et al 2005. Surfactant at various conc's was combined with this estrogenic mixt.	Harris et al 2009

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Flame Retardants (commercial mixture BDE-209)	>97% Decabromodiphenyl ether (decaBDE); Other components reported in USEPA 2008 to be: Nonabromodiphenyl ether (nonaBDE); trace amounts of Octabromodiphenyl ether (octaBDE) may be present. Component congeners in the commercial mixture were not reported.	***Development:*** (F0 exposure commenced at 8 hpf) F0: Embryo hatching rate, malformations, and mortality. Adult survival and growth, GSI, sperm density and quality, egg production F1: fertilization rate; embryo hatching rate, malformations and mortality; larval swimming response.	F0 embryos: No effects on survival, malformations, or hatching rate. F0 adults: significantly higher condition factor over control in females at ≥0.01 uM, and in males at 1 uM. All F0 female treatment groups showed decreased GSI, and males only at 1 uM. F0 sperm viability and motility were significantly reduced in all treatment groups, and sperm density reduced at ≥0.01 uM. F1 embryos: reduced hatch rate at ≥0.01 uM. F1 larvae: reduced free-swimming speed at ≥0.1 uM.	Not reported	Zebrafish (embryo, larva, juvenile, adult)	150 days (after fertilization of F0 fish)	Water	Nominal BDE-209 (uM): 0.001, 0.01, 0.1, 1 PLUS solvent (DMSO) control	Concentrations reported are of the commercial mixture BDE-209	He et al. 2011
Plant Hormones	B-sitosterol (BSR) (75.7%), B-sitostanol (BSN) (13%), Campesterol (CR) + Campestanol (CN) (9%), Artenols (A) (0.9%)	***Developmental:*** growth; mortality; thyroid hormones; histopathology of thyroid gland, liver, pancreas, kidneys, gonads	Elevated T3 after first 7 days of exposure; "serious" liver degeneration; reduced mean hatch time in all exposure groups; no effect on mortality, total hatchability or T4 levels	Not reported	Grayling (Embryos, larvae)	28 days	Water	Control, Mean measured component conc's (ug/L) at low (1 ug/L), medium (10 ug/L), and high (50 ug/L) nominal mixture conc's: BSR: 1.24, 7.2, 30.9 BSN: 0.44, 3.01, 13.75 CR: 0.24, 0.73, 3.1 CN: nd, 0.31, 1.1 A: nd, 0.16, 0.24	Mixture called Ultrasitosterol	Honkanen et al. 2005

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Hormones	Estrone (E1), 17B-estradiol (E2)	***Mortality; Growth; Reproductive:*** GSI, serum Vitellogenin, serum E2 ***Genotoxicity:*** Gonadal DNA damage ***Metabolic/Physiologic:*** EROD activity	No mortality or body weight effects were observed. Increasing trend with exposure level in vitellogenin expression. Significantly elevated (over controls) serum E2 and gonadal DNA damage. Significantly decreased EROD activity and GSI.	For each chemical component, absolute responses and responses relative to controls were similar to the mixture for all endpoints	Goldfish (M)	14 days	Water	E1: 0, 16.9, 36.3, 66.8, 141.4, 281.9 ng/L E2: 9.7, 18.6, 38.5, 71.1, 145.9 ng/L Mixture E1/E2: 9.8/4.0, 18.3/9.1, 34.9/18.0, 68.5/37.7, 137.6/75.0 ng/L	Fixed ratio design – 2:1 ratio of E1 to E2 at each exposure level of the mixture	Hua et al. 2013
WWTP effluent	Effluent complex mixture contains 17a-ethinylestradiol (EE2) measured at ‹0.5 ng/L to 2.0 ng/L, EE2 was also tested individually in fish	***Growth (EE2 study, only):*** Total length and weight, condition factor; ***Reproductive:*** Serum Vitellogenin (effluent and EE2 studies), and egg production (EE2 study, only)	Elevated vitellogenin in rainbow trout exposed to all effluent dilution treatments; elevated Vitellogenin in carp at ≥25% effluent.	Reduced growth and condition factor in males at ≥10 ng/L and in females at 100 ng/L. Elevated vitellogenin in males and females at ≥1 ng/L. elevated egg production at 0.1 and 1 ng/l, but depressed production at 10 ng/L, and elimination of egg production at 100 ng/L	Effluent: Rainbow trout (immature M only), carp (immature M only); EE2 only: Fathead minnows (adult M&F)	Effluent: 28 days EE2 only: 21 days	Water	*In situ* continuous flow study – Percent Effluent (dilutions with river water): 12.5, 25, 50, 100% , plus two negative controls (dechlorinated tap water, and river water) Controlled lab study - EE2: 0, 0.1, 1, 3, 10, 100 ng/L	Treated sewage effluent from Chelmsford, Essex, UK, was previously confirmed to contain a variety of environmental estrogens, including EE2, BPA, alkylphenols. Snails also tested *in situ*.	Jobling et al. 2004
Estrogenic Chemicals (alkylphenol, phthalate, plasticizer)	Bisphenol A (BPA), Di(2-ethylhexyl) phthalate (DEHP), Nonylphenol (NP)	***Metabolism/Physiology*** Metabolomics: Energy and lipid metabolism in liver and gonad; 46 metabolites in liver, and 48 in gonad	Metabolic signature differs between liver and gonad in mixture exposures. Metabolic stress response to mixture exposure not predicted from exposure to individual CECs; not simply additive	Metabolic signature differs between liver and gonad, and between individually tested CECs.	Goldfish (M)	10 days	Water	BPA: 1550 ng/L DEHP: 2050 ng/L NP: 223.5 ng/L	Apparently, the same exposure concentrations were used in the mixture and single CEC studies	Jordan et al. 2012

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (alkylphenol, hormones)	Nonylphenol (NP), 17a-ethinylestradiol (EE2), 17B-estradiol (E2)	***Mortality:*** Adult survival***;*** ***Reproductive***: GSI, egg production per day, spawning success ***Developmental:*** Hatching and embryo/larval mortality tracked for 5 weeks post-exposure	No effects on adult survival or GSI. Exposure-related decreasing trend, and significantly reduced total egg production, fecundity, spawning success, and testicular steroid release in the high exposure group. Significant increasing trend in male whole body vitellogenin with exposure level.	EE2 only: Identical results as in mixture study,	Japanese Medaka (adult M&F)	14 days	Water	Fixed ratio mixture, nominal low, medium, and high treatment levels (ng/L) – NP: 100, 500, 5000 E2: 4, 20, 200 EE2: 3.59, 17.9, 179 Estimated equipotent estradiol concentrations equivalent to total mixture estrogenicity (ng/L) – EE2 only: 76, 379, 3793	Authors conclude: Estrogenicity good model for predicting only some reproductive responses; and simple additive model may not predict all responses	Jukosky et al. 2008
Binary mixture (plasticizer, perfluorinated compound)	Bisphenol A (BPA), Perfluorooctane sulfonate (PFOS)	***Developmental:*** Post hatch survival and growth; malformations; histopathology in liver, gonad, thyroid; F1 and F2 fecundity and fertilization rate; vitellogenin in the tail	100% deformations and mortality observed in F2 post-hatch in all mixtures that include 300 ug/L PFOS. Reduced post-fertilization growth in nearly all F1/F2, M&F treatment groups. Exposure-related reduction in Vitellogenin in all high-PFOS mixture groups. Hepatocellular vacuolization and inflammation in high-PFOS mixtures. F1 fertilization rate and F2 fecundity reduced in high- BPA mixture groups.	Too many findings to document here. Generally, PFOS more toxic than BPA; BPA results are reported in fish ecotox database	Zebrafish	Multi-generation study	Water	Single-CEC studies – nominal exposure concentrations (ug/L) BPA: 0, 10, 200, 400 PFOS: 0, 0.6, 100, 300 In mixture study, were a total of six treatment groups, plus a negative control BPA/PFOS: 10/0.6, 10/300, 200/0.6, 200/300, 400/0.6, 400/300	Study intended to test toxicity-enhancing potential of PFOS, but authors conclude that PFOS does not consistently enhance BPA toxicity	Keiter et al. 2012

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Flame Retardants (commercial mixture BDE-209)	>97% Decabromodiphenyl ether (decaBDE); Other components reported in USEPA 2008 to be: Nonabromodiphenyl ether (nonaBDE); trace amounts of Octabromodiphenyl ether (octaBDE) may be present. Specific congeners of trace nonaBDE and octaBDE were not specified.	***Growth:*** Daily otolith increment as an index of growth	Otolith increment widths were significantly narrowed due to exposure only in the highest exposure group, compared to control, but were no different from control prior to exposure. No other effects were reported.	Not reported.	Lake whitefish (juvenile)	30 days	Diet	Nominal mixture concentrations in the feed (ug/g diet): 0, 0.1, 1, 2	Concentrations reported are of the commercial mixture BDE-209	Kuo et al 2010
Binary mixture (plasticizer, alkylphenol)	Bisphenol A (BPA), Nonylphenol (NP)	***Reproductive:*** Vitellogenin mRNA, gonad histology	vitellogenin mRNA expression, testicular enzyme induction, necrosis, and degeneration	High exposure groups showed similar effects as those seen in mixture groups	Swordtail fish (adults)	3 days	Water	Single-CEC BPA: 0, 0.4, 2, 10 mg/L NP: 0, 4, 20, 100 ug/L Mixture: BPA: 0.4 mg/L NP: 4 ug/L	NP more potent than BPA. Each CEC more potent in Vitellogenin mRNA expression in a mixture than individually	Kwak et al. 2001
Binary mixture (plasticizer, alkylphenol)	Bisphenol A (BPA), Nonylphenol (NP)	***Growth; Reproductive:*** Vitellogenin mRNA, gonad histology,	Decreasing trend in sword growth. No effect on body length	Decreasing trend in sword growth same as those seen in mixture groups	Swordtail fish (juveniles M only)	60 days	Water	Single-CEC BPA: 0, 0.2, 2, 20 ug/L NP: 0, 0.2, 2, 20 ug/L Mixture (ug/L) BPA/NP: 0.2/0.2. 2/2		Kwak et al. 2001

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (alkylphenol, hormone)	Nonylphenol (NP), 17a-ethinylestradiol (EE)	***Developmental:*** 60 days post-hatch: survival, sex ratio, gametogenesis, whole body vitellogenin induction, heat shock protein expression At 240 days post-hatch: egg production, % viability, % hatchability, % swim-up success, GSI, growth	Survival unaffected by treatments. Highly skewed sex ratio toward females in all exposure groups. In EE10 groups, NP showed concentration-related antagonistic behavior on vitellogenin induction. More egg production was observed in EE1+NP100 group than in the EE1 only group. Oogenesis was additively suppressed	Too much information to record here – see "Mixture" column for important differences and interactions	Zebrafish (M&F embryo/ larva)	60 days (F1 reproduc-tive success tested 180 days after exposure ceased)	Water	Nominal single CEC exposures NP: 0, 10, 100 ug/L EE: 0, 1, 10 ng/L Nominal mixture exposures EE(ng/L)/NP(ug/L) 0/0, 1/10, 1/100, 10/10, 10/100	CEC effects were clearly non-additive in the mixture for several endpoints Static with renewal every 48 hours.	Lin and Janz 2006
Pharmaceuticals (antiepileptic, lipid treatment, B-blocker, antibiotics)	Carbamazepine (CBZ), Fenofibric acid (FA), Propranolol hydrochloride (PHO), Sulfamethoxazole (SMX), Trimethoprim (TMP)	***Developmental:*** Growth, survival, hatching time, hatching rate, deformations, movements, heart rate	Survival, hatching time, hatching rate, and spontaneous movement were not affected by mixture exposures. No deformations in control groups, but reduced tail length, spinal deformation, and yolk sac edema occurred in concentration-related manner in treatment groups. Heart rates at 48, 72, and 96 hours exposure were significantly reduced in both mixture groups. Tail length reduction was concentration-related.	Not reported	Zebrafish (embryo/ larva)	4 days	Water	Mixture A – nominal concentrations (ng/L) CBZ: 178 FA: 70.3 PHO: 3.18 SMX: 53.3 TMP: 15.7 Plus blank and solvent controls Mixture B nominal (ug/L) (10,000x mixture A) CBZ: 1780 FA: 703 PHO: 31.8 SMX: 533 TMP: 157		Madureira et al. 2011a

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals (antiepileptic, lipid treatment, B-blocker, antibiotics)	Carbamazepine (CBZ), Fenofibric acid (FA), Propranolol hydrochloride (PHO), Sulfamethoxazole (SMX), Trimethoprim (TMP)	***Reproductive:*** GSI, gametogenesis, gonad histopathology	Shifts from mature late stage to immature stage gametes were observed in males and females. Oocyte atresia was elevated in both mixture exposure levels. No effect on GSI was observed in either mixture group.	Spermatogenesis was altered in all but the TMP exposure group. No effect on GSI was observed in any group.	Zebrafish (M&F adult)	21 days	Water	Mixture A – nominal concentrations (ng/L) CBZ: 178 FA: 70.3 PHO: 3.18 SMX: 53.3 TMP: 15.7 Plus blank and solvent controls Single chemical exposures, and Mixture B nominal (ug/L) (10,000x mixture A) CBZ: 1780 FA: 703 PHO: 31.8 SMX: 533 TMP: 157		Madureira et al. 2011b

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals (antiepileptic, lipid treatment, B-blocker, antibiotics)	Carbamazepine (CBZ), Fenofibric acid (FA), Propranolol hydrochloride (PHO), Sulfamethoxazole (SMX), Trimethoprim (TMP)	***Growth; Mortality; Behavior; Histopathology:*** Liver ***Gross Pathology:*** Liver mass, HSI ***Metabolic/Physiology:*** Liver enzyme activation	Low exposure mixture: decreased liver volume in females; males had increased eosinophilia in the liver; slight increase in vitellogenin High exposure mixture: decreased liver volume in females; males had increased eosinophilia and basophilia in the liver; increased vitellogenin Mortality, degree of swimming activity, body length and weight, condition factor, and liver enzymes were not affected by mixture exposures	Decreased liver volume was observed in females only after SMX and TMP exposures, but increased liver volume was seen in females after CBZ, FA and PHO exposures. In males, all treatments resulted in hepatomegaly. HIS was increased in males after PHO and TMP exposures and in females exposed to PHO. PHO and FA showed slightly increased vitellogenin. Significant mortality and reduced movements only in PHO group.	Zebrafish (M&F adult)	21 days	Water	Mixture A – nominal concentrations (ng/L) CBZ: 178 FA: 70.3 PHO: 3.18 SMX: 53.3 TMP: 15.7 Plus blank and solvent controls Single chemical exposures, and Mixture B nominal (ug/L) (10,000x mixture A) CBZ: 1780 FA: 703 PHO: 31.8 SMX: 533 TMP: 157		Madureira et al. 2012

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (steroidal hormones)	Estrone (E1), 17B-Estradiol (E2), 17a-ethinylestradiol (EE2)	***Behavioral:*** predator avoidance – latency, velocity, total response	In exposed embryos, at 12 days post-hatch, no statistically significant alterations in latency, velocity, or total response. In exposed larvae, at 12 days post-hatch, significantly increased latency period and a significant declining trend in total response.	In exposed embryos, at 12 days post-hatch significant declining trend in total response in E1-exposed fish, but not in other CEC groups. In exposed larvae, at 12 days post-hatch, significant declining trend in total response after 17B-estradiol exposure, but not in other CEC groups.	Fathead minnows (embryos and larvae)	Embryos: 5 days Larvae: 12 days	Water	Nominal treatment levels (ng/L): E1: 5, 50, 100 E2: 1, 10, 28 EE2: 0.1, 1, 10 Mixture E1/E2/EE2 (ng/L): Low: 5/1/0.1 Med: 50/10/1 High: 100/28/10 Plus blank and solvent controls		McGee et al. 2009
Binary Mixture	Nonylphenol monoethoxylate (NP1EO) (54%), Nonylphenol diethoxylate (NP2EO) (44%), Nonylphenol triethoxylate (NP3EO) (2%)	***Growth:*** Tail length, wet weight, condition factor (CF) ***Developmental:*** Testis-ova, ratio phenotypic male/females	No effects on growth variables. No effect on male/female ratio, and no testis-ova observed in males	Not reported	Japanese medaka (embryo/ larva/ juvenile)	100 days	Water	Nominal concentration of the mixture (ug/L): 0, 25, 50, 100	Mixture is a commercial formulation: POE (1-2) nonylphenol	Metcalfe et al. 2001
Binary Mixture	Nonylphenol Mono-ethoxycarboxylate (NP1EC) (62%), Nonylphenol diethoxycarboxylate (NP2EC) (38%)	***Growth:*** Tail length, wet weight, condition factor (CF) ***Developmental:*** Testis-ova, ratio phenotypic male/females	Reduced tail length in high exposure group and increased CF in both treatment groups. No effect on male/female ratio, and no testis-ova observed in males	Not reported	Japanese medaka (embryo/ larva/ juvenile)	100 days	Water	Nominal concentration of the mixture (ug/L): 0, 50, 100	Mixture synthesized by author's team	Metcalfe et al. 2001

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals (antidepressants)	Fluoxetine (FLX), Sertraline (SER), Venlafaxine (VEN), Bupropion (BUP)	***Growth:*** Body length ***Behavioral:*** predator avoidance – latency, velocity, total response	Embryo exposures: Neither body length nor latency period were significantly affected. The mixture exposure resulted in decreasing trends in velocity and total escape response, with significantly reduced response in these two endpoints in the high exposure group. Larva exposures: Significantly reduced body size in high exposure group. No concentration-related effects on behavioral endpoints.	Embryo exposures: No effects were seen in any sertraline or bupropion treatment groups. Significant decreasing trends in velocity and total escape response were seen for fluoxetine. Increased latency and decreased total escape response were seen in venlafaxine. None of the CECs affected body length. Larvae exposures: No effects after sertraline or fluoxetine exposures. Decreasing trend in total escape response for venlafaxine and bupropion. Elevated body length in bupropion high exposure group, and increased latency in venlafaxine high exposure group.	Fathead minnows (embryos and larvae)	Embryos: 5 days Larvae: 12 days	Water	Nominal single CEC exposures (ng/L): FLX: 0, 25, 125, 250 SER: 0, 25, 125, 250 VEN: 0, 500, 2500, 5000 BUP: 0, 200, 1000, 2000 Nominal mixture exposures (FLX/SER/VEN/BUP) (ng/L): Low: 25/25/500/200 Med: 125/125/2500/1000 High: 250/250/5000/2000	Mixtures used the same concentrations as single chemical exposures at low, med, high exposure levels	Painter et al. 2009

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals (plus 1 PCP)	Naproxen, Gemfibrozil, Diclofenac, Ibuprofen, Triclosan, Salicylic acid, Acetaminophen	***Mortality;*** ***Growth:*** Weight, length, condition factor (CF) ***Reproductive:*** Secondary sex characteristics, gonadal sex steroids egg production, ***Developmental*** hatch rate, larval survival, growth, HSI, GSI ***Circulatory/Blood:*** hematocrit	No effects on growth variables, HSI, GSI, egg production, external sex characteristics, sex hormones, egg production, egg hatch, or fry survival. Increased prevalence of deformities at the 100 and 300 ng/L levels of exposure, but not at 1000 ng/L..	Not reported	Fathead minnows	Life cycle	Water	Nominal total mixture concentrations (ng/L) (individual CEC conc's not reported for all exposure groups; ratios also not reported): blank control, solvent control, 10, 30, 100, 300, 1000		Parrott and Bennie 2009
Pharmaceuticals (NSAID, SSRI, antibiotic)	Ibuprofen (IBU), Fluoxetine (FLU), Ciprofloxacin (CP)	***Mortality***	Mortality in low, medium and high exposure groups was 0% after 35 days, 47% after 35 days and 100% after 4 days exposure, respectively. No other endpoints were reported.	Not reported, but all responses to mixtures occurred at concentrations "well below equivalent pharmacologically active concentrations in mammals".	Pumpkin-seed sunfish	35 days	Water	Fixed ratio mixture exposure groups (ug/L) of IBU/CP/FLU Low: 6, 10, 10 Med: 60, 100, 100 High: 600, 1000, 1000 PLUS negative control group	Microcosm study – multiple taxa exposure; only fish results included here, and mortality was only endpoint included in the paper	Richards et al. 2004

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (hormones, alkyl phenol)	Estrone (E1), 17B-estradiol (E2), 4-nonylphenol (NP)	***Growth:*** Length, weight ***Gross Pathology:*** HSI ***Reproductive:*** GSI, egg production, fertilization success, plasma Vitellogenin ***Developmental:*** Embryonic development, hatchability, survival, and malformation prevalence in offspring	Fertilization success was significantly reduced and embryo mortality elevated in the high exposure group. Significantly increased cumulative mortality, aggressive behavior and HIS seen in exposed parental fish. Decrease in CF seen in high-exposure females. Highly elevated plasma Vitellogenin in both treatment groups. Larval survival and malformation prevalence were not affected.	Not reported	Brown trout (adult M&F)	150 days, until the onset of spawning	Water	Mean measured CEC concentrations in mixture (E1/E2/NP) (ng/L): Low exposure: 14.0/2.1/111.0 High exposure: 56.6/7.0/1006.5	Mixture CECs selected based on the judgment that they are predominantly responsible for observed estrogenicity in river waters; selected ratios similar to those measured in the field (E1/E2/NP):	Schubert et al. 2008
Pharmaceuticals (antidepressants)	Fluoxetine (FLX), Sertraline (SER), Venlafaxine (VEN), Bupropion (BUP)	***Mortality; Growth***: Length, weight, condition factor (CF) ***Reproductive:*** Secondary sex characteristics, plasma Vitellogenin, spermatogenesis, testicular histopathology, GSI ***Organ Pathology:*** HIS, liver histopathology ***Behavior:*** Nest defense, nest occupation	No effects were reported for any endpoint in either mixture exposure group.	Significant mortality in both VEN groups, and SER high exposure group. Only the FLX high exposure group showed significant Vitellogenin induction. Secondary sex characteristics differed between groups. No effects on HSI, GSI, CF, liver histopathology, spermatogenesis, or nest behavior in any group.	Fathead minnow (adult M)	21 days	Water	Mean single CEC exposures (ng/L): FLX: 0, 2.5, 28 SER: 0, 1.6, 5.2 VEN: 0, 305, 1104 BUP: 0, 7.4, 57 Nominal mixture exposures (FLX/SER/VEN/BUP) (ng/L): Low: 2.2/1.3/117/50 High: 28/22/798/466		Schultz et al. 2011

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Personal care products (antimicrobials)	Triclosan (TCS), Triclocarban (TCC)	***Mortality;*** ***Growth:*** Weight, length, condition factor (CF) ***Organ Pathology:*** HIS, liver histopathology ***Behavior:*** Larval escape behavior, adult aggression assay ***Reproductive (adult):*** Vitellogenin induction, GSI, secondary sex characteristics, gonad histopathology	Larvae: no effects on growth or escape behavior variables Adults: mean total aggression index was severely reduced in both mixture groups. No effects on survival, growth, CF, GSI, HSI, sex characteristics, histopathology, plasma vitellogenin	Larvae: no effects on growth or escape behavior variables Adults: reduced total aggression index in both TCC groups, and the TCS low exposure group, but not in TCS high exposure group No effects on survival, growth, CF, GSI, HSI, sex characteristics, histopathology, plasma vitellogenin	Fathead minnow (M&F adults, larvae)	Larvae: 12 days Adults: 21 days	Water	Adults – single CEC mean exposures (ng/L): TCS: 0, 172, 449 TCC: 0, 560, 1576 Adults – mixture: reported that same mean conc's used for low and high mixture exposure groups Larvae – reported that same exposure groups/ conc's were used as with adults	Larvae study: static renewal Adult study: flow-through	Schultz et al. 2012
Phytoestrogens (common in wood pulp mill effluent)	B-sitosterol, genistein	***Reproductive:*** Sex hormone levels (genistein only), GSI, sperm concentration and motility, fertilization success	No effects reported.	No effects on GSI, sperm quantity or quality, sex hormone levels, or fertilization success	Fighting Fish (adult M)	21 days	Water	Single CEC exposures (ug/L): Both CECs: 0, 1 Mixture: same exposure levels	Positive control was 17B-estradiol	Stevenson et al. 2011

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Binary mixtures (estrogenic hormone and antiestrogenic pharmaceuticals)	17B-estradiol (E2) + Letrozole (LET), or Tamoxifen (TAM)	***Mortality;*** ***Growth:*** Length, weight, condition factor (CF) ***Gross Pathology***: HSI ***Reproductive:*** Plasma Vitellogenin, GSI, eggs spawned, eggs fertilized ***Developmental:*** Hatchability, gross abnormalities	Vitellogenin elevated in E2/LET males and reduced in females in all mixture groups. Egg production reduced in LET and TAM mixtures. Fertility reduced in LET-high, and all TAM groups. GSI increased in TAM-med and TAM-high but not LET groups. HIS increased in LET-low and –med, but not LET-high or TAM groups. 0% spawn seen in TAM-high. TAM-med and LET-high groups showed 100% and 71% males in F1. TAM-med also showed severe decline in hatchability, increased time to hatch, and excessively high gross abnormality rate in larvae (42.2%).	E2 alone: No effect on mortality, growth variables, GSI. Significant increase in HSI and plasma Vitellogenin in males. Significant reductions in egg production and fertility.	Japanese medaka (breeding pairs)	21 days	Water	E2 alone: 0, 200 ng/L PLUS binary mixtures of E2 (200 ng/L) with LET or TAM (ug/L) at each exposure level: 10, 50, 250 PLUS solvent and tap water controls	E2 induced "impairments in reproductive performance …[that] became more severe" in mixtures with antiestrogens	Sun et al. 2009

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Pharmaceuticals (psychoactive drugs: SSRI, SNRI, anticonvulsant)	Fluoxetine (FLX), Venlafaxine (VNX), Carbamazepine (CBZ)	***Genetic:*** Gene expression patterns	Autism spectrum disorder (ASD) gene expression patterns were enriched/ up-regulated in nearly all gene sets evaluated. No consistent patterns for sets associated with other neurological disorders.	Not reported.	Fathead minnow	Not reported.	Water	Mixture CEC nominal exposures (ug/L): FLX: 10 VNX: 50 CBZ: 100	Tested 12 sets of genes associated with human idiopathic ASD, secondary autism, Alzheimer's, Parkinson's, schizophrenia, multiple sclerosis, major depression, bipolar, and ADHD were evaluated. An additional 10 sets were evaluated for ASD	Thomas and Klaper 2012
Pharmaceuticals (psychoactive drugs: SSRI, SNRI, anticonvulsant)	Fluoxetine (FLX), Venlafaxine (VNX), Carbamazepine (CBZ)	***Behavioral:*** Predator avoidance test ***Genetic:*** Gene expression	Expression of genes known to be involved in neuron development, regulation, and growth were altered, accompanied by behavioral changes. The greatest induction occurring in the mixture group.		Fathead minnow (juvenile, indeterminate sex)	18 days	Water	Single CEC nominal exposures (ug/L): FLX: 10 VNX: 50 CBZ: 100 Mixture: All three at same concentrations PLUS control		Thomas et al. 2012

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Estrogenic Chemicals (steroidal hormones)	Estrone (E1), 17B-Estradiol (E2), 17a-ethinylestradiol (EE2)	***Mortality; Reproduction***: Plasma Vitellogenin	No significant mortality. Exposure-related increase in plasma vitellogenin; E2 and EE2 additive	No significant mortality. Each showed an exposure-related increase in vitellogenin.	Rainbow trout (female juvenile)	14 days	Water	Single CECs nominal (ng/L) – relative potency test: E1: 1, 3.2, 10, 32, 100, 320 E2: 1, 3.2, 10, 32, 100, 320 EE2: 0.1, 0.32, 1, 3.2, 10, 32 Plus, blank and solvent controls Mixture study – nominal (ng/L): E2 only: 1, 10, 25, 175, 750 EE2 only: 0.04, 0.4, 1, 7, 30 Combined E2/EE2: 5/0.2, 12.5/0.5, 87.5/3.5 Blank and solvent controls		Thorpe et al. 2003
WWTP Effluent	Complex Mixture	***Mortality; Growth; Reproduction***: Secondary sex chars, GSI, plasma Vitellogenin	The NOEC for Vitellogenin ranged between <25% to 25% effluent in males, and 25% to 100% in females. Vitellogenin responses were proportional to measured conc's of estradiol and estrone in the effluents. GSI elevated in males at ≥50%, but not in females. No effects on survival or growth in M or F, or M secondary sex characteristics were observed.	Not applicable.	Fathead minnow (M&F)	21 days	Water	Dilution levels of WWTP effluent from each of three different WWTPs: 0, 25, 50, and 100% effluent from WWTPs with Low, Medium, and High anticipated estrogenic potential. PLUS a dilution water control		Thorpe et al. 2008

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Bleach kraft mill effluent	Complex Mixture	***Growth:*** Condition factor ***Reproductive:*** GSI, plasma vitellogenin, plasma testosterone and pregnenolone ***Gross Pathology:*** HSI ***Metabolic:*** hepatic mixed-function oxidase activity ***Blood/Circulatory:*** plasma cholesterol	Effects observed were: decreased HSI in high exposure group of PM2 effluent; increased vitellogenin in high group of PM1 effluent; decreased pregnenolone at ≥35% PM1 and PM2 effluent; and increased liver MFO activity at ≥10% effluent. No effects were observed in other endpoints.	Not Applicable	Rainbow Trout (juvenile)	21 days	Water	Dilution levels of bleach-kraft mill effluent from each of two different mills, which were designated PM1 and PM2 in the paper: 0, 10, 35, and 70% effluent PLUS a control		Tremblay and Van Der Kraak 1999
Binary Mixture (plasticizer, alkylphenol)	Bisphenol A (BPA), Nonylphenol (NP)	***Developmental:*** Embryo survival, hatch rates, developmental abnormalities, and oxidative stress metrics	No differences from controls in embryo survival, hatch rates, or developmental abnormalities in any mixture group No effects on hydroxyl radical formation. But increased MDA in high exposure group, and decreased GSH, GSSG, GR, CAT, SOD, Gpx, GST, and ALP in all mixture treatment groups.	No differences from controls in embryo survival, hatch rates, or developmental abnormalities in any single CEC treatment group. Hydroxyl radical formation and/or MDA content elevated at ≥100 ug/L BPA and ≥10 ug/L NP. Decreased GSH, GSSG, GR, CAT, SOD, Gpx, GST, and ALP in nearly all single CEC treatment groups	Zebrafish (embryos)	7 days	Water	Single CECs (nominal ug/L): NP: 0, 0.1, 1, 10, 100 BPA: 0, 0.1, 1, 10, 100, 1000 mixture exposure levels – nominal BPA/NP ug/L): Low: 1/1 Medium: 10/10 High: 100/100 PLUS solvent (DMSO) and tap water controls		Wu et al. 2011

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
Binary Mixture (plasticizer, alkylphenol)	Bisphenol A (BPA), Nonylphenol (NP)	***Developmental:*** Embryo oxidative stress metrics	Mixture exposure results were similar to single-chemical results.	Total reactive oxygen species, NO, and NOS were elevated at ≥100 ug/L BPA and ≥10 ug/L NP. Levels of 8 cytokines and expression of 6 Toll-like receptors were altered from controls in most single-CEC treatment groups.	Zebrafish (embryos)	7 days	Water	Single CECs (nominal ug/L): NP: 0, 0.1, 1, 10, 100 BPA: 0, 0.1, 1, 10, 100, 1000 mixture exposure levels – nominal BPA/NP ug/L): Low: 1/1 High: 10/10 PLUS solvent (DMSO) and tap water controls		Xu et al. 2013
Flame Retardants (PBDEs)	contains tetra- and penta-brominated diphenyl ethers (BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154)	***Mortality; Growth; Endocrine:*** Serum T3 and T4 ***Developmental:*** F0 and F1 survival, hatch rate, body weights, and % malformations	No effects on survival were observed in any exposure group. Decreased hatch rates and body weights were observed in all F1 groups (exposed and non-exposed), but not in the F0 group. Increased malformation rates only observed in F1 groups exposed to ≥3 ug/L. T4 significantly increased in high exposure groups, both F0 and F1.	Not reported	Zebrafish (embryo, larvae, adult)	multiple generations: F0: 150 days; F1: 10 d	Water	F0 exposed from embryo to adult: 0, 1, 3, 10 ug/L of the mixture DE-71; F1 divided into two groups: Non-exposed F1, and F1 groups exposed at same concentrations as parents	Commercial mixture DE-71	Yu et al. 2011

ATTACHMENT 3-1 (continued)

CEC Category	Mixture Component CECs	***Effect Category***; Endpoints Evaluated	Effects		Exposure				Notes	Reference
			Mixture	Single Chemicals	Fish Species	Duration	Route	Concentrations (measured values, when reported in paper)		
PPCPs	Atenolol, Caffeine, Diphenhydramine Gemfibrozil, DEET, Ibuprofen, Naproxen, Triclosan, Triclocarban	***Mortality;*** ***Growth:*** whole body weight, total length, condition factor; ***Reproductive:*** GSI; ***Gross Pathology:*** hepatic- and brain-somatic indexes; ***Endocrine:*** Expression in 10 receptor genes (including for Vitellogenin)	No effects on mortality rate, growth, condition factor, HSI, or GSI were observed. Downregulation of Vitellogenin receptor gene expression in females (no Vitellogenin effect in males), and downregulation of 3 other receptor gene expressions in males	No effects on mortality rate, growth, condition factor or GSI were observed. Triclocarban: Up-regulation of vitellogenin receptor gene in males and females, and alteration of two additional receptor gene expressions in males. DEET: slight decrease in HSI in females. Downregulation of one in ten hormone receptor gene expressions, only in females	Fathead minnows (M&F adult)	2 days	Water	Single CEC mean measured (ug/L): DEET: 0.6 Triclocarban: 0.79 Mixture CEC measured (ug/L): Triclocarban: 0.71 Triclosan: 1.39 Ibuprofen: 0.34 Naproxen: 1.1 Atenolol: 1.34 Caffeine: 0.25 DEET: 0.54 Diphenhydramine: 0.07 Gemfibrozil: 1.21		Zenobio et al. 2014

ATTACHMENT 3-2. Database for derivation of Chemical Complexity Uncertainty Factor (UF_{CC}) point estimates calculated from comparison of mixture and single-CEC laboratory study results in fish (this is an abridged version; the electronic database includes all fields listed in Section 3.2.4). Sections 3.2.5 and 3.2.6 describe how the fields in this table are used to derive UF_{CC} values. Records are organized alphabetically by publication reference.

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	17a-ethinylestradiol	Mortality	Percent Mortality	Y	Fathead Minnow	0.00025	11.9	0.00025	28.6	47600.000	114400.000	2.403	Armstrong et al. 2015
Hormone	Estrone	Reproductive	Reproductive (serum Vitellogenin)	N	Goldfish	0.282	210	0.138	400	744.681	2898.551	3.892	Hua et al 2013
Hormone	17B-estradiol	Reproductive	Reproductive (serum Vitellogenin)	N	Goldfish	0.146	325	0.075	400	2226.027	5333.333	2.396	Hua et al 2013
Hormone	Estrone	Reproductive	Reproductive (GSI)	Y	Goldfish	0.282	1.45	0.138	1.3	5.142	9.420	1.832	Hua et al 2013
Hormone	17B-estradiol	Reproductive	Reproductive (GSI)	Y	Goldfish	0.146	1.35	0.075	1.3	9.247	17.333	1.875	Hua et al 2013
Hormone	Estrone	Genotoxicity	Genotoxicity (gonad DNA damage)	N	Goldfish	0.282	4.6	0.138	5.7	16.312	41.304	2.532	Hua et al 2013
Hormone	17B-estradiol	Genotoxicity	Genotoxicity (gonad DNA damage)	N	Goldfish	0.146	5.1	0.075	5.7	34.932	76.000	2.176	Hua et al 2013
Hormone	Estrone	Physiologic/ Metabolic	Metabolic (liver EROD activity)	N	Goldfish	0.2820	11	0.1380	11	39.007	79.710	2.043	Hua et al 2013
Hormone	17B-estradiol	Physiologic/ Metabolic	Metabolic (liver EROD activity)	N	Goldfish	0.1460	12.5	0.0750	11	85.616	146.667	1.713	Hua et al 2013

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	17B-estradiol	Mortality	Percent Mortality	Y	Japanese medaka	2.5280	56	0.2418	56	22.152	231.596	10.455	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (total egg production)	Y	Japanese medaka	2.5280	10	0.2418	20.5	3.956	84.781	21.433	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (fecundity: eggs/day)	Y	Japanese medaka	2.5280	0.38	0.2418	1.46	0.150	6.038	40.169	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (male GSI)	Y	Japanese medaka	2.5280	0.37	0.2418	0.19	0.146	0.786	5.369	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (female GSI)	Y	Japanese medaka	2.5280	0.88	0.2418	0.4	0.348	1.654	4.752	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (spawning success)	Y	Japanese medaka	2.5280	1	0.2418	3	0.396	12.407	31.365	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (ovarian testosterone release)	Y	Japanese medaka	2.5280	18	0.2418	19	7.120	78.577	11.036	Jukosky et al. 2008
Hormone	17B-estradiol	Reproductive	Reproductive (testicular testosterone release)	Y	Japanese medaka	2.5280	20	0.2418	22	7.911	90.984	11.500	Jukosky et al. 2008
Plasticizer	Bisphenol A	Mortality	% Mortality	Y	Zebrafish	400.0	18	400.0	18	0.045	0.045	1.000	Keiter et al 2012
Plasticizer	Bisphenol A	Mortality	% Mortality	Y	Zebrafish	400.0	18	400.0	25	0.045	0.063	1.389	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Mortality	% Mortality	Y	Zebrafish	300.0	19	300.0	25	0.063	0.083	1.316	Keiter et al 2012
Plasticizer	Bisphenol A	Mortality	Mortality	Y	Zebrafish	400.0	15	400.0	30	0.038	0.075	2.000	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Mortality	Mortality	Y	Zebrafish	0.6	19	0.6	30	31.667	50.000	1.579	Keiter et al 2012

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population-Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	Mortality	Mortality	Y	Zebrafish	400.0	9	400.0	20	0.023	0.050	2.222	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Mortality	Mortality	Y	Zebrafish	0.6	19	0.6	20	31.667	33.333	1.053	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (length)	Y	Zebrafish	400.0	38	400.0	35	0.095	0.088	1.086	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (length)	Y	Zebrafish	300.0	36	300.0	35	0.120	0.117	1.029	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (length)	Y	Zebrafish	400.0	32	400.0	31	0.080	0.078	1.032	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (length)	Y	Zebrafish	0.6	34	0.6	31	56.667	51.667	1.097	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (length)	Y	Zebrafish	400.0	39	400.0	37	0.098	0.093	1.054	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (length)	Y	Zebrafish	400.0	39	400.0	36	0.098	0.090	1.083	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (length)	Y	Zebrafish	300.0	37	300.0	36	0.123	0.120	1.028	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (length)	Y	Zebrafish	400.0	31	400.0	31	0.078	0.078	1.000	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (length)	Y	Zebrafish	0.6	32	0.6	31	53.333	51.667	1.032	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (weight)	Y	Zebrafish	400.0	490	400.0	320	1.225	0.800	1.531	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (weight)	Y	Zebrafish	300.0	405	300.0	320	1.350	1.067	1.266	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (weight)	Y	Zebrafish	400.0	280	400.0	275	0.700	0.688	1.018	Keiter et al 2012

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population-Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (weight)	Y	Zebrafish	0.6	320	0.6	275	533.333	458.333	1.164	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (weight)	Y	Zebrafish	400.0	645	400.0	545	1.613	1.363	1.183	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (weight)	Y	Zebrafish	400.0	645	400.0	520	1.613	1.300	1.240	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (weight)	Y	Zebrafish	300.0	555	300.0	520	1.850	1.733	1.067	Keiter et al 2012
Plasticizer	Bisphenol A	Growth	Growth (weight)	Y	Zebrafish	400.0	255	400.0	255	0.638	0.638	1.000	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Growth	Growth (weight)	Y	Zebrafish	0.6	320	0.6	255	533.333	425.000	1.255	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Histopathology	Histopathology (prevalence hepatocellular vacuolization)	N	Zebrafish	300.0	24	300.0	45	0.080	0.150	1.875	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Histopathology	Histopathology (hepatocellular granuloma histological index)	N	Zebrafish	300.0	2.45	300.0	3.8	0.008	0.013	1.551	Keiter et al 2012
Flame Retardant / Surfactant	Perfluorooctane sulfonate	Reproductive	Reproductive (fertilization rate)	Y	Zebrafish	300.0	80	300.0	73	0.267	0.243	1.096	Keiter et al 2012
Alkylphenol	Nonylphenol	Developmental	Developmental (sex ratio of 60d old larvae, as % female)	Y	Zebrafish	100.0	100	100.0	85	1.000	0.850	1.176	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (sex ratio of 60d old larvae, as % female)	Y	Zebrafish	0.01	90	0.01	85	9000.000	8500.000	1.059	Lin and Janz 2006

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population-Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Alkylphenol	Nonylphenol	Reproductive	Reproductive (whole body Vitellogenin, M+F)	N	Zebrafish	100.0	0.5	100.0	7.5	0.005	0.075	15.000	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Reproductive	Reproductive (whole body Vitellogenin, M+F)	N	Zebrafish	0.01	15	0.01	7.5	1500.000	750.000	2.000	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (larval length)	Y	Zebrafish	100.0	13	100.0	10	0.130	0.100	1.300	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (larval length)	Y	Zebrafish	0.01	9.1	0.01	10	910.000	1000.000	1.099	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (larval weight)	Y	Zebrafish	100.0	16.5	100.0	7.8	0.165	0.078	2.115	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (larval weight)	Y	Zebrafish	0.01	6.3	0.01	7.8	630.000	780.000	1.238	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (larval condition index)	Y	Zebrafish	100.0	0.78	100.0	0.76	0.008	0.008	1.026	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (larval condition index)	Y	Zebrafish	0.01	0.84	0.01	0.76	84.000	76.000	1.105	Lin and Janz 2006
Alkylphenol	Nonylphenol	Reproductive	Reproductive (mean number eggs produced)	Y	Zebrafish	100.0	150	100.0	35	1.500	0.350	4.286	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Reproductive	Reproductive (mean number eggs produced)	Y	Zebrafish	0.01	40	0.01	35	4000.000	3500.000	1.143	Lin and Janz 2006
Alkylphenol	Nonylphenol	Reproductive	Reproductive (percent viable eggs)	Y	Zebrafish	100.0	73	100.0	65	0.730	0.650	1.123	Lin and Janz 2006

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	17a-ethinylestradiol	Reproductive	Reproductive (percent viable eggs)	Y	Zebrafish	0.01	50	0.01	65	5000.000	6500.000	1.300	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (hatchability)	Y	Zebrafish	0.01	63	0.01	81	6300.000	8100.000	1.286	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (percent swim-up)	Y	Zebrafish	100.0	70	100.0	68	0.700	0.680	1.029	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (percent swim-up)	Y	Zebrafish	0.01	58	0.01	68	5800.000	6800.000	1.172	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (sex ratio of adults exposed as larvae, as % female)	Y	Zebrafish	100.0	75	100.0	92	0.750	0.920	1.227	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (sex ratio of adults exposed as larvae, as % female)	Y	Zebrafish	0.01	91	0.01	92	9100.000	9200.000	1.011	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (length of adults exposed as larvae)	Y	Zebrafish	100.0	39.3	100.0	37.6	0.393	0.376	1.045	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (length of adults exposed as larvae)	Y	Zebrafish	0.01	38.1	0.01	37.6	3810.000	3760.000	1.013	Lin and Janz 2006
Alkylphenol	Nonylphenol	Developmental	Developmental (weight of adults exposed as larvae)	Y	Zebrafish	100.0	631	100.0	484	6.310	4.840	1.304	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (weight of adults exposed as larvae)	Y	Zebrafish	0.01	535	0.01	484	53500.000	48400.000	1.105	Lin and Janz 2006

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population-Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Alkylphenol	Nonylphenol	Developmental	Developmental (condition index of adults exposed as larvae)	Y	Zebrafish	100.0	1.02	100.0	0.87	0.010	0.009	1.172	Lin and Janz 2006
Hormone	17a-ethinylestradiol	Developmental	Developmental (GSI index in adult males exposed as larvae)	Y	Zebrafish	0.01	0.01	0.01	0.011	1.000	1.100	1.100	Lin and Janz 2006
Pharmaceutical - anticonvulsant	Carbamazepine (CBZ)	Gross Pathology	Gross Pathology (hepatomegaly in M)	N	Zebrafish	1780.0	5.84	1780.0	5.86	0.003	0.003	1.003	Madureira et al 2012
Pharmaceutical - anti-cholesterol	Fenofibric Acid (FA)	Gross Pathology	Gross Pathology (hepatomegaly in M)	N	Zebrafish	703.0	5.95	703.0	5.86	0.008	0.008	1.015	Madureira et al 2012
Pharmaceutical - beta blocker	Propranolol Hydrochloride (PHO)	Gross Pathology	Gross Pathology (hepatomegaly in M)	N	Zebrafish	31.8	7.69	31.8	5.86	0.242	0.184	1.312	Madureira et al 2012
Pharmaceutical - antibiotic	Sulfamethoxazole (SMX)	Gross Pathology	Gross Pathology (hepatomegaly in M)	N	Zebrafish	533.0	5.95	533.0	5.86	0.011	0.011	1.015	Madureira et al 2012
Pharmaceutical - antibiotic	Trimethoprim (TMP)	Gross Pathology	Gross Pathology (hepatomegaly in M)	N	Zebrafish	157.0	6.7	157.0	5.86	0.043	0.037	1.143	Madureira et al 2012
Pharmaceutical - anticonvulsant	Carbamazepine (CBZ)	Gross Pathology	Gross Pathology (hepatomegaly in F)	N	Zebrafish	1780.0	35.53	1780.0	21.65	0.020	0.012	1.641	Madureira et al 2012
Pharmaceutical - anti-cholesterol	Fenofibric Acid (FA)	Gross Pathology	Gross Pathology (hepatomegaly in F)	N	Zebrafish	703.0	33.4	703.0	21.65	0.048	0.031	1.543	Madureira et al 2012
Pharmaceutical - beta blocker	Propranolol Hydrochloride (PHO)	Gross Pathology	Gross Pathology (hepatomegaly in F)	N	Zebrafish	31.8	37.23	31.8	21.65	1.171	0.681	1.720	Madureira et al 2012
Pharmaceutical - antibiotic	Sulfamethoxazole (SMX)	Gross Pathology	Gross Pathology (hepatomegaly in F)	N	Zebrafish	533.0	24.78	533.0	21.65	0.046	0.041	1.145	Madureira et al 2012
Pharmaceutical - antibiotic	Trimethoprim (TMP)	Gross Pathology	Gross Pathology (hepatomegaly in F)	N	Zebrafish	157.0	27.75	157.0	21.65	0.177	0.138	1.282	Madureira et al 2012

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
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Hormone	Estrone (E1)	Behavioral	Behavioral (larval escape latency period)	Y	Fathead Minnow	0.100	73	0.100	130	730.000	1300.000	1.781	McGee et al 2009
Hormone	17B-estradiol (E2)	Behavioral	Behavioral (larval escape latency period)	Y	Fathead Minnow	0.028	65	0.028	130	2321.429	4642.857	2.000	McGee et al 2009
Hormone	17a-ethinylestradiol (EE2)	Behavioral	Behavioral (larval escape latency period)	Y	Fathead Minnow	0.010	110	0.010	130	11000.000	13000.000	1.182	McGee et al 2009
Hormone	Estrone (E1)	Behavioral	Behavioral (larval total escape response)	Y	Fathead Minnow	0.100	0.0045	0.100	0.0019	0.045	0.019	2.368	McGee et al 2009
Hormone	17B-estradiol (E2)	Behavioral	Behavioral (larval total escape response)	Y	Fathead Minnow	0.028	0.0038	0.028	0.0019	0.136	0.068	2.000	McGee et al 2009
Hormone	17a-ethinylestradiol (EE2)	Behavioral	Behavioral (larval total escape response)	Y	Fathead Minnow	0.010	0.0025	0.010	0.0019	0.250	0.190	1.316	McGee et al 2009
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Behavioral	Behavioral (embryonic escape velocity)	Y	Fathead Minnow	0.25	0.01	0.25	0.0085	0.040	0.034	1.176	Painter et al 2009
Pharmaceutical - antidepressant	Setraline (SER)	Behavioral	Behavioral (embryonic escape velocity)	Y	Fathead Minnow	0.25	0.0138	0.25	0.0085	0.055	0.034	1.624	Painter et al 2009
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Behavioral	Behavioral (embryonic escape velocity)	Y	Fathead Minnow	5.00	0.008	5.00	0.0085	0.002	0.002	1.063	Painter et al 2009
Pharmaceutical - antidepressant	Bupropion (BUP)	Behavioral	Behavioral (embryonic escape velocity)	Y	Fathead Minnow	2.00	0.0135	2.00	0.0085	0.007	0.004	1.588	Painter et al 2009

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Behavioral	Behavioral (embryonic total escape response)	Y	Fathead Minnow	0.25	0.0038	0.25	0.003	0.015	0.012	1.267	Painter et al 2009
Pharmaceutical - antidepressant	Setraline (SER)	Behavioral	Behavioral (embryonic total escape response)	Y	Fathead Minnow	0.25	0.0055	0.25	0.003	0.022	0.012	1.833	Painter et al 2009
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Behavioral	Behavioral (embryonic total escape response)	Y	Fathead Minnow	5.00	0.0028	5.00	0.003	0.001	0.001	1.071	Painter et al 2009
Pharmaceutical - antidepressant	Bupropion (BUP)	Behavioral	Behavioral (embryonic total escape response)	Y	Fathead Minnow	2.00	0.0048	2.00	0.003	0.002	0.002	1.600	Painter et al 2009
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Developmental	Developmental (larval body length)	Y	Fathead Minnow	0.25	7.3	0.25	7.5	29.200	30.000	1.027	Painter et al 2009
Pharmaceutical - antidepressant	Setraline (SER)	Developmental	Developmental (larval body length)	Y	Fathead Minnow	0.25	7.8	0.25	7.5	31.200	30.000	1.040	Painter et al 2009
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Developmental	Developmental (larval body length)	Y	Fathead Minnow	5.00	7	5.00	7.5	1.400	1.500	1.071	Painter et al 2009
Pharmaceutical - antidepressant	Bupropion (BUP)	Developmental	Developmental (larval body length)	Y	Fathead Minnow	2.00	8.3	2.00	7.5	4.150	3.750	1.107	Painter et al 2009
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Behavioral	Behavioral (larval escape latency period)	Y	Fathead Minnow	5.00	147	5.00	110	29.400	22.000	1.336	Painter et al 2009
Pharmaceutical - antidepressant	Bupropion (BUP)	Behavioral	Behavioral (larval escape velocity)	Y	Fathead Minnow	2.00	0.008	2.00	0.01	0.004	0.005	1.250	Painter et al 2009
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Behavioral	Behavioral (larval total escape response)	Y	Fathead Minnow	5.00	0.0022	5.00	0.0035	0.000	0.001	1.591	Painter et al 2009

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Pharmaceutical - antidepressant	Setraline (SER)	Mortality	% Mortality (adult males)	Y	Fathead Minnow	0.005	27	0.022	1	5400.000	45.455	118.800	Schultz et al 2011
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Mortality	% Mortality (adult males)	Y	Fathead Minnow	1.104	22	0.798	1	19.928	1.253	15.902	Schultz et al 2011
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Reproductive	Reproductive (adult male plasma vitellogenin)	N	Fathead Minnow	0.028	17.78	0.028	9.55	635.000	341.071	1.862	Schultz et al 2011
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Reproductive	Reproductive (testicular interstitial cell prominence)	N	Fathead Minnow	0.028	2	0.028	1.75	71.429	62.500	1.143	Schultz et al 2011
Pharmaceutical - antidepressant	Fluoxetine (FLX)	Reproductive	Reproductive (adult male secondary sex characteristics index)	N	Fathead Minnow	0.028	0.53	0.028	0.45	18.929	16.071	1.178	Schultz et al 2011
Pharmaceutical - antidepressant	Setraline (SER)	Reproductive	Reproductive (adult male secondary sex characteristics index)	N	Fathead Minnow	0.005	0.47	0.022	0.45	94.000	20.455	4.596	Schultz et al 2011
Pharmaceutical - antidepressant	Venlafaxine (VEN)	Reproductive	Reproductive (adult male secondary sex characteristics index)	N	Fathead Minnow	1.104	0.47	0.798	0.45	0.426	0.564	1.325	Schultz et al 2011
Pharmaceutical - antidepressant	Bupropion (BUP)	Reproductive	Reproductive (adult male secondary sex characteristics index)	N	Fathead Minnow	0.057	0.49	0.466	0.45	8.596	0.966	8.902	Schultz et al 2011
Personal Care - antimicrobial	Triclosan (TS)	Behavioral	Behavioral (adult male total aggression (nest defense) index)	Y	Fathead Minnow	0.45	5	0.45	0.1	11.111	0.222	50.000	Schultz et al 2012
Personal Care - antimicrobial	Triclocarban (TC)	Behavioral	Behavioral (adult male total aggression (nest defense) index)	Y	Fathead Minnow	1.60	0.1	1.60	0.1	0.063	0.063	1.000	Schultz et al 2012

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population-Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Personal Care - antimicrobial	Triclosan (TS)	Behavioral	Behavioral (larval escape velocity)	Y	Fathead Minnow	0.45	0.095	0.45	0.13	0.211	0.289	1.368	Schultz et al 2012
Personal Care - antimicrobial	Triclocarban (TC)	Behavioral	Behavioral (larval escape velocity)	Y	Fathead Minnow	1.60	0.095	1.60	0.13	0.059	0.081	1.368	Schultz et al 2012
Hormone	17B-estradiol (E2)	Gross Pathology	Gross Pathology (adult male HSI)	N	Japanese medaka	0.187	3	0.187	2	16.043	10.695	1.500	Sun et al 2009
Hormone	17B-estradiol (E2)	Gross Pathology	Gross Pathology (adult male HSI)	N	Japanese medaka	0.187	3	0.187	1.75	16.043	9.358	1.714	Sun et al 2009
Hormone	17B-estradiol (E2)	Gross Pathology	Gross Pathology (adult female HSI)	N	Japanese medaka	0.187	4	0.187	3.25	21.390	17.380	1.231	Sun et al 2009
Hormone	17B-estradiol (E2)	Gross Pathology	Gross Pathology (adult female HSI)	N	Japanese medaka	0.187	4	0.187	3.5	21.390	18.717	1.143	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (adult male GSI)	Y	Japanese medaka	0.187	0.65	0.187	1.1	3.476	5.882	1.692	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (adult male plasma vitellogenin)	N	Japanese medaka	0.187	5000	0.187	3500	26737.968	18716.578	1.429	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (adult male plasma vitellogenin)	N	Japanese medaka	0.187	5000	0.187	250	26737.968	1336.898	20.000	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (adult female plasma vitellogenin)	N	Japanese medaka	0.187	12000	0.187	1000	64171.123	5347.594	12.000	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (adult female plasma vitellogenin)	N	Japanese medaka	0.187	12000	0.187	500	64171.123	2673.797	24.000	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (fecundity)	Y	Japanese medaka	0.187	12.5	0.187	7.5	66.845	40.107	1.667	Sun et al 2009

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (fecundity)	Y	Japanese medaka	0.187	12.5	0.187	11	66.845	58.824	1.136	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (fertility)	Y	Japanese medaka	0.187	19	0.187	15	101.604	80.214	1.267	Sun et al 2009
Hormone	17B-estradiol (E2)	Reproductive	Reproductive (fertility)	Y	Japanese medaka	0.187	19	0.187	20	101.604	106.952	1.053	Sun et al 2009
Hormone	17B-estradiol (E2)	Developmental	Developmental (hatchability - %)	Y	Japanese medaka	0.187	74.9	0.187	43.1	400.535	230.481	1.738	Sun et al 2009
Hormone	17B-estradiol (E2)	Developmental	Developmental (time to hatch - days)	Y	Japanese medaka	0.187	8.57	0.187	9.07	45.829	48.503	1.058	Sun et al 2009
Hormone	17B-estradiol (E2)	Developmental	Developmental (sex ratio, as % male)	Y	Japanese medaka	0.187	52	0.187	100	278.075	534.759	1.923	Sun et al 2009
Hormone	17B-estradiol (E2)	Developmental	Developmental (sex ratio, as % male)	Y	Japanese medaka	0.187	52	0.187	71	278.075	379.679	1.365	Sun et al 2009
Hormone	17B-estradiol (E2)	Developmental	Developmental (prevalence gross larval abnormalities - %)	Y	Japanese medaka	0.187	2	0.187	42.2	10.695	225.668	21.100	Sun et al 2009
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (hydroxyl radical formation)	N	Zebrafish	100.0	140	100.0	110	1.400	1.100	1.273	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (hydroxyl radical formation)	N	Zebrafish	100.0	135	100.0	110	1.350	1.100	1.227	Wu et al. 2011

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (MDA content)	N	Zebrafish	100.0	125	100.0	145	1.250	1.450	1.160	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (MDA content)	N	Zebrafish	100.0	130	100.0	145	1.300	1.450	1.115	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GSH content)	N	Zebrafish	100.0	30	100.0	10	0.300	0.100	3.000	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GSH content)	N	Zebrafish	100.0	15	100.0	10	0.150	0.100	1.500	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GSSG content)	N	Zebrafish	100.0	50	100.0	40	0.500	0.400	1.250	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GSSG content)	N	Zebrafish	100.0	50	100.0	40	0.500	0.400	1.250	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GR activity)	N	Zebrafish	100.0	60	100.0	30	0.600	0.300	2.000	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GR activity)	N	Zebrafish	100.0	40	100.0	30	0.400	0.300	1.333	Wu et al. 2011

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (CAT activity)	N	Zebrafish	100.0	60	100.0	45	0.600	0.450	1.333	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (CAT activity)	N	Zebrafish	100.0	50	100.0	45	0.500	0.450	1.111	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (SOD activity)	N	Zebrafish	100.0	40	100.0	10	0.400	0.100	4.000	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (SOD activity)	N	Zebrafish	100.0	20	100.0	10	0.200	0.100	2.000	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Gpx activity)	N	Zebrafish	100.0	70	100.0	45	0.700	0.450	1.556	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Gpx activity)	N	Zebrafish	100.0	50	100.0	45	0.500	0.450	1.111	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GST activity)	N	Zebrafish	100.0	43	100.0	38	0.430	0.380	1.132	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (GST activity)	N	Zebrafish	100.0	41	100.0	38	0.410	0.380	1.079	Wu et al. 2011

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic /Physiologic - Oxidative Stress (ALP activity)	N	Zebrafish	100.0	68	100.0	48	0.680	0.480	1.417	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (ALP activity)	N	Zebrafish	100.0	48	100.0	48	0.480	0.480	1.000	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total glutathione content)	N	Zebrafish	100.0	11.52	100.0	7.34	0.115	0.073	1.569	Wu et al. 2011
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total glutathione content)	N	Zebrafish	100.0	9.98	100.0	7.34	0.100	0.073	1.360	Wu et al. 2011
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total reactive oxygen species as % of control)	N	Zebrafish	10.0	115	10.0	150	11.500	15.000	1.304	Xu et al 2013
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total reactive oxygen species as % of control)	N	Zebrafish	10.0	135	10.0	150	13.500	15.000	1.111	Xu et al 2013

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total Nitric Oxide as % of control)	N	Zebrafish	10.0	115	10.0	120	11.500	12.000	1.043	Xu et al 2013
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total Nitric Oxide as % of control)	N	Zebrafish	10.0	115	10.0	120	11.500	12.000	1.043	Xu et al 2013
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total Nitric Oxide Synthase as % of control)	N	Zebrafish	10.0	110	10.0	125	11.000	12.500	1.136	Xu et al 2013
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Total Nitric Oxide Synthase as % of control)	N	Zebrafish	10.0	115	10.0	125	11.500	12.500	1.087	Xu et al 2013
Plasticizer	Bisphenol A	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Inducible Nitric Oxide Synthase as relative mRNA level)	N	Zebrafish	10.0	0.7	10.0	1.8	0.070	0.180	2.571	Xu et al 2013

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Alkylphenol	Nonylphenol	Physiologic/ Metabolic	Metabolic/ Physiologic - Oxidative Stress (Inducible Nitric Oxide Synthase as relative mRNA level)	N	Zebrafish	10.0	1.5	10.0	1.8	0.150	0.180	1.200	Xu et al 2013
Personal Care - antimicrobial	Triclocarban (TCC)	Genotoxicity	Genotoxicity (relative gene expression in males - gonad androgen receptor (ar))	N	Fathead Minnow	0.8	0.5	0.7	0.75	0.633	1.056	1.669	Zenobio et al 2014
Personal Care - antimicrobial	Triclocarban (TCC)	Genotoxicity	Genotoxicity (relative gene expression in males - gonad thyroid hormone receptor (thra1))	N	Fathead Minnow	0.8	1.9	0.7	0.7	2.405	0.986	2.439	Zenobio et al 2014
Insect Repellent	DEET	Genotoxicity	Genotoxicity (relative gene expression in males - gonad thyroid hormone receptor (thra1))	N	Fathead Minnow	0.6	1.1	0.5	0.7	1.833	1.296	1.414	Zenobio et al 2014
Personal Care - antimicrobial	Triclocarban	Genotoxicity	Genotoxicity (relative gene expression in males - gonad steroidogenic acute regulatory protein (star))	N	Fathead Minnow	0.8	0.25	0.7	0.45	0.316	0.634	2.003	Zenobio et al 2014

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Insect Repellent	DEET	Genotoxicity	Genotoxicity (relative gene expression in males - gonad steroidogenic acute regulatory protein (star))	N	Fathead Minnow	0.6	1.2	0.5	0.45	2.000	0.833	2.400	Zenobio et al 2014
Personal Care - antimicrobial	Triclocarban	Genotoxicity	Genotoxicity (relative gene expression in males - liver vitellogenin (vitellogenin))	N	Fathead Minnow	0.8	2.6	0.7	0.6	3.291	0.845	3.895	Zenobio et al 2014
Personal Care - antimicrobial	Triclocarban	Genotoxicity	Genotoxicity (relative gene expression in males - liver lipoprotein lipase (lpl))	N	Fathead Minnow	0.6	2	0.5	0.75	3.333	1.389	2.400	Zenobio et al 2014
Personal Care - antimicrobial	Triclocarban	Genotoxicity	Genotoxicity (relative gene expression in females - liver vitellogenin (vitellogenin))	N	Fathead Minnow	0.8	2.1	0.7	0.1	2.658	0.141	18.873	Zenobio et al 2014
Insect Repellent	DEET	Genotoxicity	Genotoxicity (relative gene expression in females - liver vitellogenin (vitellogenin))	N	Fathead Minnow	0.6	0.5	0.5	0.1	0.833	0.185	4.500	Zenobio et al 2014

ATTACHMENT 3-2. (continued)

UF_{CC} STUDY ATTRIBUTES						COMPARISON INFORMATION				COMPUTATIONS			Publication Reference
CEC Category	CEC	Effect Category	Effect Endpoint	Population -Relevant Endpoint (Y/N)	Species	High Exposure Group CEC Concentration (ppb) for Single CEC Assay	High Exposure Group Effect Magnitude for CEC in Single CEC Assay	High Exposure Group CEC Concentration (ppb) for CEC in Mixture Assay	High Exposure Group Effect Magnitude for CEC in Mixture Assay	Single CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC1)	Mixture CEC Assay - Effect Magnitude per unit Exposure at High Exposure Conc. (EPUC2)	UF_{CC} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Insect Repellent	DEET	Genotoxicity	Genotoxicity (relative gene expression in females - gonad androgen receptor (ar))	N	Fathead Minnow	0.6	0.45	0.5	1.25	0.750	2.315	3.086	Zenobio et al 2014

ATTACHMENT 3-3. Database for derivation of Inter-species Sensitivity Uncertainty Factor (UF_{Inter}) point estimates calculated from comparison of toxicity effect results in two fish species (this is an abridged version; the electronic database includes all fields listed in Section 3.3.4). Sections 3.3.5 and 3.3.6 describe how the fields in this table are used to derive UF_{Inter} values. Records are organized alphabetically by publication reference.

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Pharmaceutical - Nonsteroidal Aromatase Inhibitor	Fadrazole	Reproductive	% max cumulative egg production	Y	Fathead Minnow	100	0.08	Medaka	100	0.02	0.0008	0.0002	4.00	Celander et al. 2011
Pharmaceutical - Nonsteroidal Aromatase Inhibitor	Fadrazole	Reproductive	% max cumulative egg production	Y	Fathead Minnow	100	0.08	Zebrafish	100	0.38	0.0008	0.0038	4.75	Celander et al. 2011
Pharmaceutical - Nonsteroidal Aromatase Inhibitor	Fadrazole	Reproductive	% max cumulative egg production	Y	Medaka	100	0.02	Zebrafish	100	0.38	0.0002	0.0038	19.00	Celander et al. 2011
Fungicide	Prochloraz	Reproductive	% max cumulative egg production	Y	Fathead Minnow	20	0.70	Medaka	100	0.1	0.0350	0.0010	35.00	Celander et al. 2011
Fungicide	Prochloraz	Reproductive	% max cumulative egg production	Y	Fathead Minnow	20	0.70	Zebrafish	100	0.48	0.0350	0.0048	7.29	Celander et al. 2011

ATTACHMENT 3-3. (continues)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Fungicide	Prochloraz	Reproductive	% max cumulative egg production	Y	Medaka	100	0.10	Zebrafish	100	0.48	0.0010	0.0048	4.80	Celander et al. 2011
Fungicide	Prochloraz	Reproductive	vitellogenin	N	Fathead Minnow	100	60	Medaka	100	10	0.6000	0.1000	6.00	Celander et al. 2011
Fungicide	Prochloraz	Reproductive	vitellogenin	N	Fathead Minnow	100	60	Zebrafish	100	40	0.6000	0.4000	1.50	Celander et al. 2011
Fungicide	Prochloraz	Reproductive	vitellogenin	N	Medaka	100	10	Zebrafish	100	40	0.1000	0.4000	4.00	Celander et al. 2011
Personal Care Product - uv filtering agent	Benzophenone-3	Reproductive	vitellogenin	N	Medaka	240	6100	Rainbow Trout	498	1100	25	2.2088	11.51	Coronado et al. 2008
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Reproductive	% DNA in sperm head	N	Brown Trout	0.02	57	Common Carp	0.01	20	2857	1987	1.44	Dietrich et al. 2007
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Genotoxicity	% fragmented DNA	N	Brown Trout	0.02	6.10	Common Carp	0.01	6.94444444	305	694	2.28	Dietrich et al. 2007
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Genotoxicity	Sperm DNA damage index	N	Brown Trout	0.02	63	Common Carp	0.01	23	3143	2286	1.38	Dietrich et al. 2007
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Reproductive	Sperm motility - curvilinear velocity	Y	Brown Trout	0.15	37	Common Carp	0.15	19	249	129	1.93	Dietrich et al. 2007
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Reproductive	Sperm motility - linearity	Y	Brown Trout	0.1	21	Common Carp	0.1	19	210	188	1.12	Dietrich et al. 2007

ATTACHMENT 3-3. (continued)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Reproductive	Sperm motility - straight line velocity	Y	Brown Trout	0.1	31	Common Carp	0.1	21	315	215	1.47	Dietrich et al. 2007
Surfactant (nonionic)	Octoxynol 9 (Triton X-100)	Reproductive	Sperm tail length	N	Brown Trout	0.05	16	Common Carp	0.05	0.19267823	327	3.8536	84.93	Dietrich et al. 2007
Surfactant (anionic)	Sodium dodecyl sulphate (SDS)	Reproductive	Sperm motility - curvilinear velocity	Y	Brown Trout	0.05	33	Common Carp	0.05	14	656	282	2.33	Dietrich et al. 2007
Herbicide	Picloram	Growth	Length	Y	Bull Trout	1180	10	Rainbow Trout	2370	7.36086176	0.0088	0.0031	2.83	Fairchild et al. 2009
Herbicide	Picloram	Growth	Weight	Y	Bull Trout	1180	26	Rainbow Trout	2370	16	0.0217	0.0067	3.22	Fairchild et al. 2009
Pharmaceutical - Beta Blocker	Propranolol	Metabolic/ Physiologic	embryonic heart rate	N	Medaka	0.1	5.43	Zebrafish	0.1	14	54	138	2.55	Finn et al 2012
Fungicide	Imidazole Ketoconazole	Metabolic/ Physiologic	Cytochrome P450 activation - liver CYP1A expression	N	Rainbow Trout	25	329	Mummichog	25	60	13	2.4173	5.44	Hegelund et al. 2004
Fungicide	Imidazole Ketoconazole	Metabolic/ Physiologic	Cytochrome P450 activation - liver CYP1A expression	N	Rainbow Trout	25	329	Mummichog	25	37	13	1.4822	8.87	Hegelund et al. 2004

ATTACHMENT 3-3. (continues)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Fungicide	Imidazole Ketoconazole	Metabolic/ Physiologic	Cytochrome P450 activation - liver CYP3A expression	N	Rainbow Trout	25	38	Mummichog	25	89	1.5082	3.5465	2.35	Hegelund et al. 2004
Fungicide	Imidazole Ketoconazole	Metabolic/ Physiologic	Cytochrome P450 activation - liver CYP3A expression	N	Rainbow Trout	25	38	Mummichog	25	91	1.5082	3.6452	2.42	Hegelund et al. 2004
Fungicide	Prochloraz	Developmental	sex ratio as percent females	Y	Fathead Minnow	301	83	Zebrafish	320	54	0.2744	0.1683	1.63	Holbech et al 2012
Fungicide	Prochloraz	Developmental	sex ratio as percent males	Y	Fathead Minnow	301	64	Zebrafish	320	9.75609756	0.2121	0.0305	6.96	Holbech et al 2012
Hormone	17B-estradiol (E2)	Mortality/ Survival	% survival	Y	Rio Grande Silvery Minnow	0.0123	39	Fathead Minnow	0.0123	53	3163	4333	1.37	Jorgenson et al. 2015
Hormone	17B-estradiol (E2)	Gross Pathology	body condition factor	N	Fathead Minnow	0.0123	15	Bluegill	0.0123	10	1251	841	1.49	Jorgenson et al. 2015
Hormone	Spironolactone	Growth	body mass	Y	Fathead Minnow	44	53	Medaka	48	25	1.2121	0.5208	2.33	LaLone et al 2013
Hormone	Spironolactone	Reproductive	GSI	Y	Fathead Minnow	44	146	Medaka	48	35	3.3217	0.7353	4.52	LaLone et al 2013
Hormone	Spironolactone	Reproductive	GSI	Y	Fathead Minnow	2.6	47	Medaka	3.3	21	18	6.3345	2.87	LaLone et al 2013

ATTACHMENT 3-3. (continued)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Hormone	Spironolactone	Reproductive	secondary sex characteristic score	Y	Fathead Minnow	44	1.95	Medaka	48	24	0.0442	0.5081	11.49	LaLone et al 2013
Hormone	Spironolactone	Reproductive	secondary sex characteristic score	Y	Fathead Minnow	2.6	104900	Medaka	3.3	522900	40346	158455	3.93	LaLone et al 2013
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	Fathead Minnow	0.01	229900	Roach	0.01	3600	22990000	360000	63.86	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	3-Spine Stickleback	0.01	850	Medaka	0.01	9900	85000	990000	11.65	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	3-Spine Stickleback	0.01	850	Zebrafish	0.01	299900	85000	29990000	352.82	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	3-Spine Stickleback	0.01	850	Rainbow Trout	0.002	5800	85000	2900000	34.12	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	Medaka	0.01	9900	Zebrafish	0.01	299900	990000	29990000	30.29	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	Medaka	0.01	9900	Rainbow Trout	0.002	5800	990000	2900000	2.93	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	Zebrafish	0.01	299900	Rainbow Trout	0.002	5800	29990000	2900000	10.34	Lange et al. 2012
Hormone	17a-Ethinylestradiol (EE2)	Reproductive	hepatic vitellogenin	N	Fathead Minnow	0.01	44	Rainbow Trout	0.01	800	4444	80000	18.00	Lange et al. 2012
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	White Sucker	3000	52	Creek Chub	3000	298	0.0174	0.0992	5.71	Oakes et al 2005

ATTACHMENT 3-3. (continues)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	White Sucker	3000	52	Spottail Shiner	3000	292	0.0174	0.0974	5.61	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	Creek Chub	3000	298	Spottail Shiner	3000	292	0.0992	0.0974	1.02	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	Creek Chub	3000	255	Spottail Shiner	3000	307	0.0848	0.1022	1.20	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	Fathead Minnow	300	373	Rainbow Trout	3000	73	1.2424	0.0244	50.86	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic fatty acyl-CoA oxidase (FAO) activity	N	Fathead Minnow	300	373	Rainbow Trout	1000	60	1.2424	0.0598	20.76	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic TBARS	N	Creek Chub	3000	59	Spottail Shiner	3000	85	0.0196	0.0285	1.45	Oakes et al 2005

ATTACHMENT 3-3. (continued)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Metabolic/ Physiologic	hepatic TBARS	N	Fathead Minnow	300	119	Rainbow Trout	1000	70	0.3958	0.0704	5.62	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Gross Pathology	Liver/Somatic Index (LSI)	N	White Sucker	3000	17	Rainbow Trout	3000	16	0.0057	0.0052	1.10	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Gross Pathology	Liver/Somatic Index (LSI)	N	White Sucker	3000	17	Rainbow Trout	1000	14	0.0057	0.0140	2.44	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Reproductive	plasma 11-ketotestosterone	N	Fathead Minnow	300	113	Rainbow Trout	3000	255	0.3772	0.0851	4.43	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Reproductive	plasma 11-ketotestosterone	N	Fathead Minnow	300	113	Rainbow Trout	1000	41	0.3772	0.0408	9.24	Oakes et al 2005
Surfactant	Perfluorooctanesulfonic acid (PFOS)	Reproductive	plasma testosterone	N	Fathead Minnow	3000	71	White Sucker	3000	33	0.0237	0.0110	2.15	Oakes et al 2005
Hormone	17a-Ethinylestradiol (EE2)	Developmental	Sex ratio (as % female)	Y	Zebrafish	0.01	49	Medaka	0.1	59	4925	589	8.36	Orn et al 2006
Hormone	17B-estradiol (E2)	Developmental	time to hatch	Y	Medaka	5000	80	Rainbow Trout	5000	105	0.0160	0.0210	1.31	Orrego et al 2011
Complex Mixture	Pulp mill effluent after primary treatment (ME2)	Developmental	time to hatch	Y	Medaka	1	115	Rainbow Trout	1	115	115	115	1.00	Orrego et al 2011
Complex Mixture	Pulp mill effluent after secondary treatment (ME3)	Developmental	time to hatch	Y	Medaka	1	80	Rainbow Trout	1	80	80	80	1.00	Orrego et al 2011
Hormone	Testosterone	Developmental	embryo mortality/ hatchability	Y	Flagfish	1000	41	Medaka	1000	35	0.0410	0.0350	1.17	Orrego et al 2011

ATTACHMENT 3-3. (continues)

UF_{Inter} STUDY ATTRIBUTES					COMPARISON INFORMATION						COMPUTATIONS			Publication Reference
CEC Category	**CEC**	**Effect Category**	**Effect Endpoint**	**Pop'n-Relevant Effect**	**Species 1**	**Species 1 - LOAEC (ug/L)**	**Species 1 - EML1 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 2**	**Species 2 - LOAEC (ug/L)**	**Species 2 - EML2 - Effect Magnitude at LOAEC (as % difference from control)**	**Species 1 - EPUC1 - Effect per unit Conc at LOAEC (EML1/ LOAEC)**	**Species 2 - EPUC2 - Effect per unit Conc at LOAEC (EML2/ LOAEC)**	**UF_{Inter} Point Estimate - Ratio of EPUCs (greater/ lesser)**	
Hormone	Testosterone	Developmental	time to hatch	Y	Medaka	1000	115	Rainbow Trout	1000	150	0.1150	0.1500	1.30	Orrego et al 2011
Complex Mixture	Pulp mill effluent - untreated (ME1)	Reproductive	sex ratio of surviving offspring, as % male	Y	Medaka	1	45	Rainbow Trout	1	65	45	65	1.45	Orrego et al 2011
Hormone	Norethindrone	Reproductive	egg production	Y	Fathead Minnow	0.0012	36	Medaka	0.022	67	30000	3030	9.90	Paulos et al 2010
Fungicide	Prochloraz	Developmental	sex ratio as % males	Y	Zebrafish	82	25	Fathead Minnow	294	27	0.3049	0.0928	3.29	Thorpe et al 2011
Fungicide	Prochloraz	Growth	total body length	Y	Zebrafish	297	9.38	Fathead Minnow	294	30	0.0316	0.1013	3.21	Thorpe et al 2011

ATTACHMENT 3-4. Characteristics of fish species included in the derivation of the UF_{Inter} values (Sources: FishBase on-line database; USFWS on-line web pages). Blank cells indicate no information was provided in the sources.

Common Name	Scientific Name	Family	Great Lakes Basin Native Species	Great Lakes Basin Resident Species	IUCN Red List Status	US Endangered Species Act or State Listed?	Niche	Forage Base	Freshwater Waterbody Type(s)	Typical Natural Habitat Features	Migratory Habits	Average Life Span (yrs)	Maximum Reported Life Span (yrs)	Average Adult Weight (g)	Maximum Adult Weight (g)	Common Adult Length (cm)	Maximum Adult Length (cm)	NOTES on Great Lakes Basin Status
Bluegill	*Lepomis macrochirus*	Centrarchidae (sunfishes)	Y	Y	Least Concern	N	benthopelagic	pelagic crustaceans, snails, small crayfish, insects, worms, small minnows	freshwater lakes, ponds, reservoirs and slow-moving streams	deep weed beds	anadromous		10		2200	19	41	plentiful, all native wild stock, can hybridize with other Lepomis spp
Brown Trout	*Salmo trutta fario*	Salmonidae (salmonids)	N	Y	Least Concern	N	pelagicneritic	aquatic and terrestrial insects; mollusks, crustaceans and small fish	large lakes, rivers during non-breeding season, swift rivers and streams during breeding	pelagic and littoral habitats	anadromous		38		5000	72	140	fully naturalized in Great Lakes; European in origin
Bull Trout	*Salvelinus confluentus*	Salmonidae (salmonids)	N	N	Vulnerable	Y	benthopelagic	terrestrial and aquatic insects, macro-zooplankton, and small fish; a wide variety of resident and anadromous fish species	large cold rivers and lakes; mountain and coastal streams	complex and connected cold, clear water types, including deep pools; clean gravel and cobble substrate	resident, land-locked migratory, or anadromous	10	>20		1450	62.5	103	non-resident in Great Lakes Basin; found in western North America

ATTACHMENT 3-4. (continued)

Common Name	Scientific Name	Family	Great Lakes Basin Native Species	Great Lakes Basin Resident Species	IUCN Red List Status	US Endangered Species Act or State Listed?	Niche	Forage Base	Freshwater Waterbody Type(s)	Typical Natural Habitat Features	Migratory Habits	Average Life Span (yrs)	Maximum Reported Life Span (yrs)	Average Adult Weight (g)	Maximum Adult Weight (g)	Common Adult Length (cm)	Maximum Adult Length (cm)	NOTES on Great Lakes Basin Status
Common Carp	*Cyprinus carpio*	Cyprinidae (minnows or carps)	N	Y	Vulnerable	N	benthopelagic	variety of benthic organisms and plant material	warm, deep, slow-flowing and still waters such as lowland rivers and large, well vegetated lakes	tolerant of poor water quality, soft sediment substrate; spawn in marginal, shallow, densely vegetated areas; larvae require very warm water among shallow submerged vegetation	potamodro-mous		38		40,100	31	120	fully naturalized in Great Lakes. Asian in origin.
Creek Chub	*Semotilus atromacul-atus*	Cyprinidae (minnows or carps)	Y	Y	Least Concern	N	demersal	small aquatic invertebrates; small fish, crayfish and other large invertebrates	headwaters, creeks and small rivers; 2intermitte nt streams	rocky and sandy pools	non-migratory		8			19.1	30.3	plentiful in the Great Lakes Basin
Fathead Minnow	*Pimephales promelas*	Cyprinidae (minnows or carps)	Y	Y	Least Concern	N	demersal	detritus and algae	headwaters, creeks, small rivers, ponds, lakes; spawns in still waters	tolerant of turbid, hot, poorly oxygenated water and intermittent streams	non-migratory		5			7.3	10.1	plentiful in the Great Lakes Basin
Flagfish	*Jordanella floridae*	Cyprinodon-tidae (pupfishes)	N	N	Not Evaluated	N	benthopelagic	worms, crustaceans, insects and plant matter	sloughs, ponds, lakes, and streams; tolerant of brackish water	vegetated areas in sluggish waters; spawn on algal-covered rocks	non-migratory						6.5	non-resident in Great Lakes Basin; found in south Florida; popular aquarium fish, so possible unsanctioned releases in Great Lakes
Japanese Medaka	*Oryzias latipes*	Adrian-ichthyidae (rice fishes)	N	N	Not Evaluated	N	benthopelagic	zooplankton and other planktivorous invertebrates	ponds, marshes, paddy fields and small flows of plains	prefer slow-moving streams; waters of lowlands, brackish water, tide pools	amphidro-mous						3.2	non-resident in Great Lakes Basin; found in Asia

ATTACHMENT 3-4. (continued)

Common Name	Scientific Name	Family	Great Lakes Basin Native Species	Great Lakes Basin Resident Species	IUCN Red List Status	US Endangered Species Act or State Listed?	Niche	Forage Base	Freshwater Waterbody Type(s)	Typical Natural Habitat Features	Migratory Habits	Average Life Span (yrs)	Maximum Reported Life Span (yrs)	Average Adult Weight (g)	Maximum Adult Weight (g)	Common Adult Length (cm)	Maximum Adult Length (cm)	NOTES on Great Lakes Basin Status
Killifish (mummichog)	*Fundulus heteroclitus*	Fundulidae (top minnows and killifishes)	N	N	Least Concern	N	benthopelagic	zooplankton, zoobenthos, fish eggs and larvae	enter fresh water to a limited extent; saltwater marshes, tidal creeks and nearby fresh water	tidal pools, marshes; resident intertidal	non-migratory		4			8.9	10.5	non-resident in Great Lakes Basin; coastal eastern US
Rainbow Trout	*Oncorhyn-chus mykiss*	Salmonidae (salmonids)	N	Y	Not Evaluated	N	benthopelagic	variety of aquatic and terrestrial invertebrates and small fishes; fish and cephalopods in the ocean	cold headwaters, creeks, small to large rivers, and lakes; coastal streams	intolerant of warm water with low DO	anadromous		11		25,40	60	122	non-native but fully naturalized; stocking continues annually in some areas
Rio Grande Silvery Minnow	*Hybog-nathus amarus*	Cyprinidae (minnows or carps)	N	N	Endangered	Y	demersal	herbivore based on gut shape; gut contents indicate will feed on algae growing on the surface of sand	fragmented reaches in the middle Rio Grande River	shallow areas with silt substrates and low or moderate water velocity , such as eddies, pools, and backwaters	non-migratory					8.7		non-resident in Great Lakes Basin; resides in the middle Rio Grande Basin of New Mexico and Texas
Roach	*Rutilus rutilus*	Cyprinidae (minnows or carps)	N	N	Least Concern	N	benthopelagic	predominantly benthic invertebrates, zooplankton, plant material, and detritus	lakes, large rivers, lowland waters	wide variety of lowland habitats, especially nutrient-rich lakes and backwaters of large to medium sized rivers; brackish water tolerant	potamodro-mous		14		1800	25	50.2	non-resident in Great Lakes Basin; resides in Europe
Spottail Shiner	*Notropis hudsonius*	Cyprinidae (minnows or carps)	Y	Y	Least Concern	N	benthopelagic	Omnivorous: insects, crustaceans, plants and algae	small to large rivers; lakes and creeks	sandy and rocky pools and runs in lotic systems; rocky and sandy shores in lakes	non-migratory		5			9	15	

ATTACHMENT 3-4. (continued)

Common Name	Scientific Name	Family	Great Lakes Basin Native Species	Great Lakes Basin Resident Species	IUCN Red List Status	US Endangered Species Act or State Listed?	Niche	Forage Base	Freshwater Waterbody Type(s)	Typical Natural Habitat Features	Migratory Habits	Average Life Span (yrs)	Maximum Reported Life Span (yrs)	Average Adult Weight (g)	Maximum Adult Weight (g)	Common Adult Length (cm)	Maximum Adult Length (cm)	NOTES on Great Lakes Basin Status
Three-spine Stickleback	*Gastero-steus aculeatus*	Gasterostidae (sticklebacks and tubesnouts)	Y	Y	Least Concern	N	benthopelagic	worms, crustaceans, larvae and adult aquatic insects, drowned aerial insects, and small fishes; cannibalize eggs and larvae	prefer small streams, but also lakes and rivers	shallow vegetated areas, usually over mud or sand	anadromous		8			5.1	11	circumpolar northern hemisphere distribution
White Sucker	*Catostomus commer-sonii*	Catostomidae (suckers)	Y	Y	Least Concern	N	demersal	zoobenthos; plankton and other small invertebrates as fry	wide variety: headwaters to large lakes; usually small creeks and rivers	prefers clear, cool waters, but tolerant of degraded conditions; feeds in shallows	potamodro-mous		12		2900	40.7	65	
Zebrafish	*Danio rerio*	Cyprinidae (minnows or carps)	N	N	Least Concern	N	benthopelagic	worms, small crustaceans, and insect larvae	canals, ditches, ponds, and lower reaches of streams	slow-moving to stagnant standing water bodies	non-migratory						3.8	non-resident in Great Lakes Basin; native to Asia

ATTACHMENT 3-5. Database for derivation of Intra-species Sensitivity Uncertainty Factor (UF_{Intra}) point estimates calculated from comparison of toxicity effect results in two different classes (defined in terms of either by life stage or sex) within a single fish species (this is an abridged version; the electronic database includes all fields listed in Section 3.4.4). Sections 3.4.5 and 3.4.6 describe how the fields in this table are used to derive UF_{Intra} values. Records are organized alphabetically by publication reference. Sex: M - male; F - female. Life Stage: E – embryo; L – larva; J – juvenile; A – adult.

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Veterinary Hormone	B-Trenbolone	N	Fathead Minnow	M	41	Reproductive	plasma E2	540.0	F	0.27	Reproductive	plasma E2	90.0	13.171	333.333	25.31	Ankley et al. 2003
Hormone	17B-Estradiol	Y	Zebrafish	L	117	Growth	Condition Factor female	20.0	J	21.6	Growth	Condition Factor male	9.7	0.171	0.448	2.62	Brion et al 2004
Hormone	17B-Estradiol	Y	Zebrafish	L	117	Growth	Condition Factor female	20.0	A	16.5	Growth	Weight female	22.3	0.171	1.351	7.90	Brion et al 2004
Hormone	17B-Estradiol	Y	Zebrafish	J	21.6	Growth	Condition Factor male	9.7	A	16.5	Growth	Weight female	22.3	0.448	1.351	3.01	Brion et al 2004
Hormone	17B-Estradiol	Y	Zebrafish	J	21.6	Reproductive	GSI male	28.6	A	82	Reproductive	GSI female	41.0	1.323	0.500	2.64	Brion et al 2004
Hormone	17B-Estradiol	Y	Zebrafish	M	0.27	Growth	Condition Factor	25.0	F	0.27	Growth	Condition Factor	10.6	92.593	39.145	2.37	Christianson-Heiska et al. 2008
Wood Extractive	Dehydroabietic Acid (DHAA)	Y	Zebrafish	M	50	Growth	Condition Factor	14.8	F	50	Growth	Condition Factor	13.0	0.295	0.260	1.14	Christianson-Heiska et al. 2008
Wood Extractive	Betulinol (BET)	Y	Zebrafish	M	5	Growth	Condition Factor	19.3	F	5	Growth	Condition Factor	16.3	3.864	3.252	1.19	Christianson-Heiska et al. 2008
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	M	0.0155	Growth	Length	23.4	F	0.0155	Growth	Length	11.9	1,506.746	769.458	1.96	Flinders et al 2014
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	L	0.0155	Mortality / Survival	% survival	9.7	J	0.0155	Mortality / Survival	% survival	34.8	624.350	2,244.039	3.59	Flinders et al 2014

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION									COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	L	0.0155	Growth	Weight	39.0	J	0.0155	Growth	Weight	30.3	2,514.650	1,954.596	1.29	Flinders et al 2014
Natural Hormone	B-sitosterol	Y	Fathead Minnow	L	22	Growth	Weight	10.0	J	70	Growth	Weight	13.9	0.453	0.199	2.28	Flinders et al 2014
Natural Hormone	B-sitosterol	Y	Fathead Minnow	L	745	Mortality / Survival	% survival	52.6	J	70	Mortality / Survival	% survival	21.7	0.071	0.311	4.40	Flinders et al 2014
Natural Hormone	B-sitosterol	Y	Fathead Minnow	L	745	Growth	Weight	16.2	J	70	Growth	Weight	13.9	0.022	0.199	9.12	Flinders et al 2014
Pharmaceuticals - Human - anticonvulsant	Carbamazepine	Y	Zebrafish	E	0.5	Mortality / Survival	% mortality	14.3	A	0.5	Reproductive	# embryos per parental female	34.6	28.571	69.231	2.42	Galus et al. 2013a
Pharmaceuticals - Human - analgesic and anti-inflammatory	Acetaminophen	Y	Zebrafish	E	0.5	Developmental	% abnormalities	980.0	A	0.5	Reproductive	# embryos per parental female	20.4	1,960.000	40.860	47.97	Galus et al. 2013a
Pharmaceuticals - Human - antidepressant	Venlafaxine	Y	Zebrafish	E	0.5	Developmental	% abnormalities	64.3	A	10	Reproductive	# embryos per parental female	59.0	128.571	5.897	21.80	Galus et al. 2013a
Pharmaceuticals - Human - lipid regulator	Gemfibrozil	Y	Zebrafish	E	0.5	Mortality / Survival	% mortality	100.0	A	0.5	Reproductive	# embryos per parental female	40.4	200.000	80.769	2.48	Galus et al. 2013a
Pharmaceuticals - Human - anticonvulsant	Carbamazepine	N	Zebrafish	M	0.5	Reproductive	plasma 11-ketotestosterone	89.4	F	0.5	Reproductive	plasma 11-ketotestosterone	62.5	178.723	125.000	1.43	Galus et al. 2013a
Hormone	17a-ethinylestradiol	N	Guppy	M	50	Neurological	brain aromatase activity	2500.0	F	50	Neurological	brain aromatase activity	145.0	50.000	2.900	17.24	Hallgren and Olsen 2009
Pharmaceuticals - Human - NSAID	Ibuprofen	Y	Japanese medaka	J	1000	Mortality / Survival	% survival	19.6	A	1	Mortality / Survival	% survival	20.5	0.020	20.541	1046.18	Han et al 2010

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Pharmaceuticals - Human - NSAID	Ibuprofen	Y	Japanese medaka	J	1000	Mortality / Survival	% survival	19.6	E	0.1	Developmental	time to hatch	34.9	0.020	348.624	17756.33	Han et al 2010
Pharmaceuticals - Human - NSAID	Ibuprofen	Y	Japanese medaka	A	1	Mortality / Survival	% survival	20.5	E	0.1	Developmental	time to hatch	34.9	20.541	348.624	16.97	Han et al 2010
Flame Retardant	DE-71	Y	Zebrafish	M	0.002	Reproductive	GSI	50.0	F	0.002	Reproductive	GSI	40.0	25,000.000	20,000.000	1.25	Han et al 2013
Flame Retardant	DE-71	Y	Zebrafish	A	0.002	Reproductive	testicular development - % spermatids	42.5	E	0.002	Developmental	% hatching	9.9	21,250.000	4,945.055	4.30	Han et al 2013
Flame Retardant	DE-71	Y	Zebrafish	A	0.002	Reproductive	testicular development - % spermatids	42.5	L	0.002	Mortality / Survival	% survival	14.0	21,250.000	6,989.247	3.04	Han et al 2013
Flame Retardant	DE-71	Y	Zebrafish	E	0.002	Developmental	% hatching	9.9	L	0.002	Mortality / Survival	% survival	14.0	4,945.055	6,989.247	1.41	Han et al 2013
Flame Retardant	BDE-209	Y	Zebrafish	M	959	Reproductive	GSI	20.0	F	0.959	Reproductive	GSI	26.1	0.021	27.202	1304.35	He et al. 2011
Flame Retardant	BDE-209	Y	Zebrafish	M	959	Growth	Condition Factor	16.7	F	959	Growth	Condition Factor	19.7	0.017	0.021	1.18	He et al. 2011
Flame Retardant	BDE-209	Y	Zebrafish	E	9.59	Developmental	% hatch	50.0	L	95.9	Behavioral	swimming speed	16.1	5.214	0.168	31.00	He et al. 2011
Flame Retardant	BDE-209	Y	Zebrafish	E	9.59	Developmental	% hatch	50.0	A	0.0959	Reproductive	GSI female	26.1	5.214	272.022	52.17	He et al. 2011
Flame Retardant	BDE-209	Y	Zebrafish	L	95.9	Behavioral	swimming speed	16.1	A	0.0959	Reproductive	GSI female	26.1	0.168	272.022	1617.39	He et al. 2011
Personal Care Product	Triclosan	N	Japanese medaka	M	136.9	Gross Pathology	HSI	24.0	F	12.8	Gross Pathology	HSI	58.1	0.175	4.536	25.88	Ishibashi et al. 2004

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Personal Care Product	Triclosan	Y	Japanese medaka	M	60.8	Reproductive	GSI	120.6	F	12.8	Reproductive	GSI	47.5	1.984	3.714	1.87	Ishibashi et al. 2004
Personal Care Product	Triclosan	Y	Japanese medaka	E	12.8	Developmental	% hatch	6.3	A	12.8	Reproductive	GSI female	47.5	0.493	3.714	7.53	Ishibashi et al. 2004
Alkyl phenols	4-Nonylphenol	Y	Japanese medaka	E	61.2	Developmental	time to hatch	40.9	A	61.2	Reproductive	mean % fertility	92.9	0.669	1.518	2.27	Ishibashi et al. 2006
Alkyl phenols	4-Nonylphenol	N	Japanese medaka	M	16.5	Gross Pathology	HSI	33.8	F	61.2	Gross Pathology	HSI	27.7	2.051	0.453	4.52	Ishibashi et al. 2006
Pharmaceuticals - Human - NSAID	Ibuprofen	N	Zebrafish	M	10	Reproductive	blood 17B-estradiol (E2)	180.0	F	10	Reproductive	blood 17B-estradiol (E2)	300.0	18.000	30.000	1.67	Ji et al 2013
Pharmaceuticals - Human - NSAID	Mefenamic Acid	N	Zebrafish	M	10	Reproductive	blood 17B-estradiol (E2)	180.0	F	10	Reproductive	blood 17B-estradiol (E2)	300.0	18.000	30.000	1.67	Ji et al 2013
Pharmaceuticals - Human - NSAID	Ibuprofen	N	Zebrafish	M	10	Reproductive	blood testosterone	30.0	F	10	Reproductive	blood testosterone	60.0	3.000	6.000	2.00	Ji et al 2013
Pharmaceuticals - Human - NSAID	Mefenamic Acid	N	Zebrafish	M	10	Reproductive	blood testosterone	50.0	F	100	Reproductive	blood testosterone	70.0	5.000	0.700	7.14	Ji et al 2013
Pharmaceuticals - Human - NSAID	Ibuprofen	N	Zebrafish	M	10	Reproductive	blood E2/testosterone ratio	350.0	F	10	Reproductive	blood E2/testosterone ratio	180.0	35.000	18.000	1.94	Ji et al 2013
Pharmaceuticals - Human - NSAID	Mefenamic Acid	N	Zebrafish	M	10	Reproductive	blood E2/testosterone ratio	500.0	F	10	Reproductive	blood E2/testosterone ratio	190.0	50.000	19.000	2.63	Ji et al 2013
Pharmaceuticals - Human - NSAID	Naproxen	N	Zebrafish	M	10	Reproductive	blood E2/testosterone ratio	100.0	F	100	Reproductive	blood E2/testosterone ratio	190.0	10.000	1.900	5.26	Ji et al 2013
Fungicide	Vinclozolin	Y	Japanese medaka	M	1000	Reproductive	% normal gonads	52.0	F	5000	Reproductive	% normal gonads	47.0	0.052	0.009	5.53	Kiparissis et al 2003

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Fungicide	Ronilan	Y	Japanese medaka	M	5000	Growth	Weight	20.9	F	5000	Growth	Weight	21.2	0.004	0.004	1.02	Kiparissis et al 2003
Fungicide	Vinclozolin	Y	Japanese medaka	M	5000	Growth	Weight	42.6	F	5000	Growth	Weight	42.5	0.009	0.009	1.00	Kiparissis et al 2003
Fungicide	Vinclozolin	Y	Japanese medaka	M	5000	Growth	Tail length	14.3	F	5000	Growth	Tail length	14.3	0.003	0.003	1.00	Kiparissis et al 2003
Hormone	cyproterone acetate (CA)	Y	Japanese medaka	M	1	Growth	Tail length	14.3	F	1	Growth	Tail length	9.5	14.286	9.524	1.50	Kiparissis et al 2003
Hormone	cyproterone acetate (CA)	Y	Japanese medaka	M	1	Growth	Weight	38.8	F	1	Growth	Weight	35.5	38.842	35.488	1.09	Kiparissis et al 2003
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	L	0.00014	Growth	Weight	5.0	A	0.58	Growth	Weight	18.8	35,913.807	32.393	1108.69	Lange et al. 2001
Hormone	Estrone (E1)	Y	Japanese medaka	M	0.005	Reproductive	GSI	1042.9	F	0.5	Reproductive	GSI	56.7	208,571.429	113.333	1840.34	Lei et al. 2013
Hormone	Estrone (E1)	Y	Japanese medaka	M	0.005	Reproductive	GSI	325.0	F	0.05	Reproductive	GSI	34.8	65,000.000	695.652	93.44	Lei et al. 2013
Hormone	Estrone (E1)	Y	Japanese medaka	E	0.047	Developmental	% hatch	7.0	A	0.46	Reproductive	GSI female	39.1	148.756	84.958	1.75	Lei et al. 2014
Hormone	Estriol (E3)	Y	Japanese medaka	M	4.5	Reproductive	GSI	300.0	F	0.46	Reproductive	GSI	39.1	66.667	84.958	1.27	Lei et al. 2014
Hormone	Estriol (E3)	Y	Japanese medaka	E	0.46	Developmental	time to hatch	13.7	A	0.46	Reproductive	GSI female	39.1	29.729	84.958	2.86	Lei et al. 2014
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Reproductive	plasma 17B-estradiol (E2)	125.0	F	1000	Reproductive	plasma 17B-estradiol (E2)	75.0	0.125	0.075	1.67	Liu et al 2012
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Reproductive	plasma testosterone (T)	30.8	F	1000	Reproductive	plasma testosterone (T)	220.0	0.031	0.220	7.15	Liu et al 2012

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Reproductive	plasma E2/T ratio	50.0	F	1000	Reproductive	plasma E2/T ratio	45.0	0.050	0.045	1.11	Liu et al 2012
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	40	Reproductive	plasma E2/11-ketotestosterone ratio	150.0	F	1000	Reproductive	plasma E2/11-ketotestosterone ratio	130.0	3.750	0.130	28.85	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Reproductive	plasma E2	150.0	F	1000	Reproductive	plasma E2	66.7	0.150	0.067	2.25	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Reproductive	plasma E2/11-ketotestosterone ratio	600.0	F	1000	Reproductive	plasma E2/11-ketotestosterone ratio	100.0	0.600	0.100	6.00	Liu et al 2012
Plasticizer	tricresyl phosphate (TCP)	N	Zebrafish	M	1000	Reproductive	testosterone	46.2	F	1000	Reproductive	testosterone	100.0	0.046	0.100	2.17	Liu et al 2012
Plasticizer	tricresyl phosphate (TCP)	N	Zebrafish	M	1000	Reproductive	plasma E2/T ratio	1500.0	F	1000	Reproductive	plasma E2/T ratio	40.0	1.500	0.040	37.50	Liu et al 2012
Plasticizer	tricresyl phosphate (TCP)	N	Zebrafish	M	1000	Reproductive	plasma E2/11-ketotestosterone ratio	350.0	F	1000	Reproductive	plasma E2/11-ketotestosterone ratio	70.0	0.350	0.070	5.00	Liu et al 2012
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	270.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	290.0	0.270	0.290	1.07	Liu et al 2012

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	180.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	220.0	0.180	0.220	1.22	Liu et al 2012
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	80.0	F	200	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	55.0	0.080	0.275	3.44	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	100.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	150.0	0.100	0.150	1.50	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	100.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	240.0	0.100	0.240	2.40	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	40	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	200.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	65.0	5.000	0.065	76.92	Liu et al 2012

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	180.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	220.0	0.180	0.220	1.22	Liu et al 2012
Flame Retardant	tris-(1,3-dichloro-2-propyl) phosphate (TDCPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	80.0	F	200	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	55.0	0.080	0.275	3.44	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	100.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	150.0	0.100	0.150	1.50	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	100.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver CYP19 mRNA	240.0	0.100	0.240	2.40	Liu et al 2012
Flame Retardant	triphenyl phosphate (TPP)	N	Zebrafish	M	40	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	200.0	F	1000	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	65.0	5.000	0.065	76.92	Liu et al 2012

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	tricresyl phosphate (TCP)	N	Zebrafish	M	40	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	50.0	F	40	Metabolic/ Physiological	gene transcription - gonad and liver CYP17 mRNA	550.0	1.250	13.750	11.00	Liu et al 2012
Plasticizer	tricresyl phosphate (TCP)	N	Zebrafish	M	200	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	60.0	F	40	Metabolic/ Physiological	gene transcription - gonad and liver Vitellogenin mRNA	60.0	0.300	1.500	5.00	Liu et al 2012
Plant Hormone	B-sitosterol	N	Goldfish	M	300	Reproductive	plasma testosterone (T)	25.0	F	300	Reproductive	plasma testosterone (T)	50.0	0.083	0.167	2.00	MacLatchy et al 1997
Pharmaceuticals - Human - anticonvulsant	Carbamazepine	N	Zebrafish	M	1780	Gross Pathology	liver volume	44.2	F	1780	Gross Pathology	liver volume	23.5	0.025	0.013	1.88	Madureira et al 2012
Pharmaceuticals - Human - anticholesterol	Fenofibric Acid	N	Zebrafish	M	703	Gross Pathology	liver volume	46.9	F	703	Gross Pathology	liver volume	16.1	0.067	0.023	2.92	Madureira et al 2012
Pharmaceuticals - Human - beta blocker - high blood pressure	Propranolol Hydrochloride	N	Zebrafish	M	31.8	Gross Pathology	liver volume	89.9	F	31.8	Gross Pathology	liver volume	29.4	2.826	0.925	3.06	Madureira et al 2012
Pharmaceuticals - Human - beta blocker - high blood pressure	Propranolol Hydrochloride	N	Zebrafish	M	31.8	Gross Pathology	HSI	50.3	F	31.8	Gross Pathology	HSI	23.5	1.582	0.738	2.15	Madureira et al 2012

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Pharmaceuticals - Human - antibiotic	Sulfamethoxazole	N	Zebrafish	M	533	Gross Pathology	liver volume	46.9	F	533	Gross Pathology	liver volume	13.9	0.088	0.026	3.38	Madureira et al 2012
Pharmaceuticals - Human - antibiotic	Trimethoprim	N	Zebrafish	M	157	Gross Pathology	liver volume	65.4	F	157	Gross Pathology	liver volume	3.5	0.417	0.023	18.46	Madureira et al 2012
Plasticizer	Bisphenol A	N	Common Carp	M	0.85	Reproductive	plasma 17B-estradiol (E2)	90.0	F	0.85	Reproductive	plasma 17B-estradiol (E2)	95.0	105.882	111.765	1.06	Mandich et al 2007
Plasticizer	Bisphenol A	N	Common Carp	M	1055	Reproductive	plasma testosterone (T)	85.7	F	1055	Reproductive	plasma testosterone (T)	81.3	0.081	0.077	1.05	Mandich et al 2007
Plasticizer	Bisphenol A	Y	Fathead Minnow	M	130	Reproductive	altered gametogenesis - relative frequencies of reproductive cell types	56.2	F	567	Reproductive	altered gametogenesis - relative frequencies of reproductive cell types	47.5	0.432	0.084	5.16	Mihaich et al 2012
Surfactant	perfluorooctane sulfonate (PFOS)	N	Fathead Minnow	M	0.3	Reproductive	plasma testosterone (T)	163.6	F	2.9	Reproductive	plasma testosterone (T)	71.1	545.455	24.521	22.24	Oakes et al 2005
Surfactant	perfluorooctane sulfonate (PFOS)	N	Fathead Minnow	M	0.3	Reproductive	plasma 11-ketotestosterone	100.0	F	0.3	Reproductive	plasma 11-ketotestosterone	113.2	333.333	377.193	1.13	Oakes et al 2005
Surfactant	perfluorooctane sulfonate (PFOS)	N	Fathead Minnow	M	2.9	Metabolic/ Physiological	hepatic TBARS	175.0	F	0.3	Metabolic/ Physiological	hepatic TBARS	118.8	60.345	395.833	6.56	Oakes et al 2005
Surfactant	perfluorooctane sulfonate (PFOS)	N	Creek Chub	M	2.9	Metabolic/ Physiological	hepatic TBARS	62.6	F	2.9	Metabolic/ Physiological	hepatic TBARS	58.7	21.593	20.244	1.07	Oakes et al 2005
Personal Care Product	Triclosan	Y	Zebrafish	E	500	Mortality / Survival	% mortality	757.1	L	500	Mortality / Survival	% mortality	350.0	1.514	0.700	2.16	Oliveira et al 2009

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Personal Care Product	Triclosan	Y	Zebrafish	E	500	Developmental	% hatch	90.9	A	300	Mortality / Survival	% mortality	3100.0	0.182	10.333	56.86	Oliveira et al 2009
Pharmaceuticals - Human - antidepressant	Venlafaxine	Y	Fathead Minnow	E	0.5	Behavioral	escape response latency period	67.1	L	5	Behavioral	escape response latency period	86.5	134.286	17.297	7.76	Painter et al. 2009
Hormone	Dihydrotestosterone (DHT)	N	Fathead Minnow	M	6	Reproductive	Secondary sex char: # nuptial tubercles	77.8	F	6	Reproductive	Secondary sex char: # nuptial tubercles	900.0	12.963	150.000	11.57	Panter et al. 2004
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Fadrazole	Y	Fathead Minnow	M	51.7	Reproductive	GSI	46.2	F	24.8	Reproductive	GSI	34.4	0.893	1.386	1.55	Panter et al. 2004
Herbicide	Trifluralin	Y	Sheepshead minnow	E	9.6	Developmental	% hatch	100.0	J	9.6	Mortality / Survival	% mortality	193.3	10.417	20.139	1.93	Parrish et al 1978
Herbicide	Trifluralin	Y	Sheepshead minnow	E	9.6	Developmental	% hatch	100.0	A	1.3	Reproductive	total # eggs spawned	23.8	10.417	18.292	1.76	Parrish et al 1978
Herbicide	Trifluralin	Y	Sheepshead minnow	J	9.6	Mortality / Survival	% mortality	193.3	A	1.3	Reproductive	total # eggs spawned	23.8	20.139	18.292	1.10	Parrish et al 1978
Pesticide	Pentachlorophenol	Y	Sheepshead minnow	E	195	Developmental	% hatch	34.0	J	195	Mortality / Survival	% mortality	460.0	0.174	2.359	13.52	Parrish et al 1978
Pesticide	Pentachlorophenol	Y	Sheepshead minnow	E	195	Developmental	% hatch	34.0	A	88	Mortality / Survival	% survival	1100.0	0.174	12.500	71.65	Parrish et al 1978
Pesticide	Pentachlorophenol	Y	Sheepshead minnow	J	195	Mortality / Survival	% mortality	460.0	A	88	Mortality / Survival	% survival	1100.0	2.359	12.500	5.30	Parrish et al 1978
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	M	0.01	Reproductive	GSI	46.2	F	0.1	Reproductive	GSI	82.8	4,615.385	828.125	5.57	Pawlowski et al 2004
Hormone	17a-ethinylestradiol	Y	Fathead Minnow	M	0.01	Growth	Condition Factor	13.6	F	0.01	Growth	Condition Factor	1.7	1,355.932	173.913	7.80	Pawlowski et al 2004

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	cyproterone acetate (CA)	N	Mummichog	F	0.25	Reproductive	plasma testosterone concentration (T)	92.1	M	0.25	Reproductive	plasma testosterone concentration (T)	48.7	368.421	194.872	1.89	Sharpe et al 2004
Hormone	17a-methyltestosterone (MT)	N	Mummichog	M	0.25	Reproductive	testosterone production (pg/mg/h)	14.7	F	0.25	Reproductive	testosterone production (pg/mg/h)	20.2	58.621	80.952	1.38	Sharpe et al 2004
Hormone	cyproterone acetate (CA)	N	Mummichog	M	0.25	Reproductive	testosterone production (pg/mg/h)	26.7	F	0.25	Reproductive	testosterone production (pg/mg/h)	14.3	106.897	57.143	1.87	Sharpe et al 2004
Hormone	17a-methyltestosterone (MT)	N	Mummichog	M	0.1	Reproductive	plasma testosterone concentration (T)	39.5	F	0.01	Reproductive	plasma testosterone concentration (T)	40.0	395.349	4,000.000	10.12	Sharpe et al 2004
Hormone	cyproterone acetate (CA)	N	Mummichog	M	0.1	Reproductive	plasma testosterone concentration (T)	20.9	F	0.01	Reproductive	plasma testosterone concentration (T)	33.3	209.302	3,333.333	15.93	Sharpe et al 2004
Hormone	17a-methyltestosterone (MT)	N	Mummichog	M	0.1	Reproductive	testosterone production (pg/mg/h)	30.4	F	0.1	Reproductive	testosterone production (pg/mg/h)	30.8	304.348	307.692	1.01	Sharpe et al 2004

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Hormone	cyproterone acetate (CA)	N	Mummichog	M	0.1	Reproductive	testosterone production (pg/mg/h)	17.4	F	0.001	Reproductive	testosterone production (pg/mg/h)	15.4	173.913	15,384.615	88.46	Sharpe et al 2004
Plasticizer	Bisphenol A	Y	Fathead Minnow	E	531	Developmental	% hatch	32.9	A	1280	Reproductive	# eggs spawned per female	93.5	0.062	0.073	1.18	Sohoni et al. 2001
Plasticizer	Bisphenol A	Y	Fathead Minnow	M	531	Growth	length	13.0	F	531	Growth	length	9.1	0.024	0.017	1.43	Sohoni et al. 2001
Plasticizer	Bisphenol A	Y	Fathead Minnow	M	531	Growth	weight	32.3	F	531	Growth	weight	31.6	0.061	0.059	1.02	Sohoni et al. 2001
Plasticizer	Bisphenol A	Y	Fathead Minnow	M	531	Reproductive	GSI	41.2	F	531	Reproductive	GSI	65.9	0.078	0.124	1.60	Sohoni et al. 2001
Plasticizer	Bisphenol A	Y	Fathead Minnow	E	160	Developmental	% hatch F2 eggs	21.7	J	1	Growth	weight F2 juveniles	11.1	0.136	11.111	81.78	Staples et al 2011
Plasticizer	Bisphenol A	Y	Fathead Minnow	E	160	Developmental	% hatch F2 eggs	21.7	A	1	Reproductive	# eggs per F1 female per day	61.5	0.136	61.538	452.92	Staples et al 2011
Plasticizer	Bisphenol A	Y	Fathead Minnow	J	1	Growth	weight F2 juveniles	11.1	A	1	Reproductive	# eggs per F1 female per day	61.5	11.111	61.538	5.54	Staples et al 2011
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Letrozole	Y	Japanese medaka	E	23.5	Developmental	% hatch	19.1	J	23.5	Developmental	F1 21-day sex ratio as % female	32.7	0.812	1.391	1.71	Sun et al 2007
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Letrozole	Y	Japanese medaka	E	23.5	Developmental	% hatch	19.1	A	23.5	Reproductive	fertility - total # eggs per mating pair per day	31.3	0.812	1.330	1.64	Sun et al 2007

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Letrozole	Y	Japanese medaka	J	23.5	Developmental	F1 21-day sex ratio as % female	32.7	A	23.5	Reproductive	fertility - total # eggs per mating pair per day	31.3	1.391	1.330	1.05	Sun et al 2007
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Letrozole	N	Japanese medaka	M	23.5	Gross Pathology	HSI	23.8	F	23.5	Gross Pathology	HSI	14.3	1.013	0.608	1.67	Sun et al 2007
Pharmaceuticals - Human - antitumor - aromatase inhibitor	Letrozole	Y	Japanese medaka	M	114.5	Reproductive	GSI	42.3	F	558.9	Reproductive	GSI	36.8	0.369	0.066	5.61	Sun et al 2007
Plasticizer	Bisphenol A	Y	Japanese medaka	E	200	Developmental	% hatch	12.9	L	200	Mortality / Survival	% survival	14.4	0.065	0.072	1.12	Sun et al 2014
Plasticizer	Bisphenol A	N	Japanese medaka	M	6	Metabolic/ Physiological	relative mRNA level of CYP11A indicating transcription of HPG axis-related gene	30.0	F	200	Metabolic/ Physiological	relative mRNA level of CYP11A indicating transcription of HPG axis-related gene	70.0	5.000	0.350	14.29	Sun et al 2014

ATTACHMENT 3-5. (continued)

UF_{Intra} STUDY ATTRIBUTES				COMPARISON INFORMATION										COMPUTATIONS			Publication Reference
CEC Category	CEC	Pop'n-Relev. Effect (Y or N)	Species Name	Class 1 (Sex: M, F; Life Stage: E,L,J,A)	Class 1 LOAEC (ug/L)	Class 1 - Effect Category at LOAEC	Class 1 - Effect Endpoint at LOAEC	Class 1 - Effect Magnitude at LOAEC (as % difference from control)	Class 2 (Sex: M, F; Life Stage: E,L,J,A)	Class 2 LOAEC (ug/L)	Class 2 - Effect Category at LOAEC	Class 2 - Effect Endpoint(s) at LOAEC	Class 2 - Effect Magnitude at LOAEC (as % difference from control)	Class 1 - EPUC1 - Effect Magnitude per unit Concentration at LOAEC	Class 2 - EPUC2 - Effect Magnitude per unit Concentration at LOAEC	UF_{Intra} Point Estimate - Ratio of EPUCs (greater/ lesser)	
Plasticizer	Bisphenol A	N	Japanese medaka	M	6	Metabolic/ Physiological	relative mRNA level of CYP11B indicating transcription of HPG axis-related gene	50.0	F	200	Metabolic/ Physiological	relative mRNA level of CYP11B indicating transcription of HPG axis-related gene	80.0	8.333	0.400	20.83	Sun et al 2014
Personal Care Product - antibacterial	Triclocarban	N	Fathead Minnow	M	0.79	Metabolic/ Physiological	relative gene expression from liver - vitellogenin	150.0	F	0.79	Metabolic/ Physiological	relative gene expression from liver - vitellogenin	100.0	189.873	126.582	1.50	Zenobio et al 2014

ATTACHMENT 4-1. Acute and chronic ecotoxicological reference values for aquatic organisms (fish; sometimes also invertebrates, plants, and/or algae) exposed to emerging contaminants in water as reported in the peer-reviewed literature, where measured and/or modeled fish ecotoxicity effect levels are included among values used to derive the reference value (sorted by CAS Number).

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
50-27-1	Estriol	PNEC	60 ng/L	Caldwell et al. 2012	All available chronic aquatic toxicity data; fish ID'd as most sensitive taxonomic group; reproduction ID'd as most sensitive endpoint group; species sensitivity distribution; $HC_{5,50}$ of NOECs
50-27-1	Estriol	PNEC	0.00075 ug/L	Carlsson et al 2006	Based on lowest among 3 chronic ecotoxicity reference values reported in studies in fish; safety factors applied
50-28-2	17β- estradiol	PNEC	2 ng/L	Caldwell et al. 2012	All available chronic aquatic toxicity data; fish ID'd as most sensitive taxonomic group; reproduction ID'd as most sensitive endpoint group; species sensitivity distribution; $HC_{5,50}$ of NOECs
50-28-2	17β- estradiol	PNEC	0.00002 ug/L	Carlsson et al 2006	Based on lowest among 2 chronic ecotoxicity reference values reported in studies in fish; safety factors applied
53-16-7	Estrone	PNEC	6 ng/L	Caldwell et al. 2012	All available chronic aquatic toxicity data; fish ID'd as most sensitive taxonomic group; reproduction ID'd as most sensitive endpoint group; species sensitivity distribution; $HC_{5,50}$ of NOECs
57-27-2	Morphine	Calc'd PNEC	257 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (257 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009

[26] AHTN - Acetyl hexamethyltetrahydronaphthalene
HHCB - Hexahydrohexamethylcyclopentabenzopyran

[27] PNEC – Predicted No Effect Concentration
Calc'd PNEC – derived by FWS – divided the reported fish acute EC50 values by 1000, following Ginebreda et al. 2009
EQS – Proposed Environmental Quality Standard (European Union)
BC-WQG – Water quality guidelines (British Columbia, Canada)
IPS – Ideal Performance Standard (Environment Canada)
Interim PWQO – Interim Provincial Water Quality Objective (Ontario Ministry of Environment and Energy)
AWQC – Aquatic Life Ambient Water Quality Criterion

[28] $HC_{5,50}$ – hazard concentration at which 5% of species may be adversely affected, estimated with 50% confidence intervals

ATTACHMENT 4-1. (continued)

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
57-63-6	17α-ethinyl estradiol	PNEC	0.35 ng/L	Caldwell et al. 2008	Based on all available chronic aquatic toxicity data - aquatic and semi-aquatic animals; literature review; data quality criteria for data included; considered all endpoints, ID'd most sensitive endpoint; species sensitivity distribution; 26 species; $HC_{5,50}$ of NOECs
57-63-6	17α-ethinyl estradiol	PNEC	0.1 ng/L	Caldwell et al. 2012	Update of 2008 paper; all available chronic aquatic toxicity data; fish ID'd as most sensitive taxonomic group; reproduction ID'd as most sensitive endpoint group; species sensitivity distribution
57-63-6	17α-ethinyl estradiol	PNEC	0.00002 ug/L	Carlsson et al 2006	Based on lowest among 2 ecotoxicity reference values reported in studies in algae and fish; safety factors applied
57-63-6	17α-ethinyl estradiol	BC-WQG	0.5 ng/L	BCME 2009	Chronic exposure guideline; 30-day concentration of 5 weekly measured unfiltered concentrations; no single measured concentration may exceed 0.75 ng/L. Based on lowest among dozens of LOECs and NOECs reported in studies is aquatic plants, invertebrates, amphibians, and fish. Safety factor of 2 applied; narrow difference between NOAEC and LOAEC
57-68-1	Sulfamethazine	Calc'd PNEC	517 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (517 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
58-08-2	Caffeine	Calc'd PNEC	805 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (805 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
58-55-9	Theophylline	Calc'd PNEC	1679 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (1679 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
59-05-2	Methotrexate	Calc'd PNEC	0.000038 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish ($3.83x10^{-5}$ mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
72-14-0	Sulfathiazole	PNEC	0.1 ug/L	Park and Choi 2008	Acute PNEC based on lowest reference value reported in acute toxicity studies in algae, invertebrates and fish; safety factor of 1000 applied
76-57-3	Codeine	Calc'd PNEC	238 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (238 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
80-05-7	Bisphenol A	PNEC	0.06 ug/L	Wright-Walters et al. 2011	Aquatic organisms (animals, plants, micro-flora and -fauna); literature review; limited evaluation to survival, growth, development, reproduction endpoints; data quality criteria applied; 24 species; $HC_{5,50}$ of NOECs
80-05-7	Bisphenol A	EQS	0.8 ng/L	Hansen 2007	EQSs derived from PNECs, which were determined by applying safety factors to NOECs with clear relevance for protecting aquatic communities

ATTACHMENT 4-1. (continued)

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
80-05-7	Bisphenol A	PNEC	0.1 ug/L	Oehlmann et al 2008	Based on lowest NOEC reported in fish toxicity studies; safety factors applied
80-05-7	Bisphenol A	Interim PWQO	5 ug/L	MOEE 1994, as cited in Hull et al. 2015	The interim provincial water quality objective (PWQO) is the threshold unfiltered concentration in water intended to be protective of aquatic life. MOEE 1994 is a secondary document; primary literature not located.
98-86-2	Acetophenone	Calc'd PNEC	181 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (181 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
103-90-2	Acetaminophen	Calc'd PNEC	258 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (258 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
104-40-5	4-Nonylphenol	EQS	3.3 ng/L	Hansen 2007	EQSs derived from PNECs, which were determined by applying safety factors to NOECs with clear relevance for protecting aquatic communities
104-40-5	4-Nonylphenol	AWQC	6.6 ug/L	USEPA 2005	National water quality criterion based on chronic ecotoxicity studies in freshwater zooplankton, macroinvertebrates, and fish. Upper bound exposure threshold not to exceed either 28 ug/l 1-hour average, or 6.6 ug/L 4-day average, more than once every three years, on average.
114-07-8	Erythromycin	Calc'd PNEC	61 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (61 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
122-11-2	Sulfadimethoxine	Calc'd PNEC	226 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (226 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
140-66-9	4-tert-Octylphenol	EQS	200 ng/L	Hansen 2007	EQSs derived from PNECs, which were determined by applying safety factors to NOECs with clear relevance for protecting aquatic communities
144-82-1	Sulfamethizole	Calc'd PNEC	1113 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (1113 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
298-46-4	Carbamazepine	PNEC	35.4 ug/L	Ginebreda et al 2009	Acute PNEC derived from a measured acute tox EC50 value for fish, by dividing the EC50 by an "arbitrary" safety factor of 1000
298-46-4	Carbamazepine	PNEC	0.5 ug/L	Ferrari et al 2004	Chronic PNEC based on lowest reference value derived from acute and reproductive toxicity data in algae and ceriodaphnia, and embryo mortality test in fish; safety factors applied
298-46-4	Carbamazepine	PNEC	0.0025 mg/L	Zhao et al 2010	Based on lowest among 5 measured chronic NOEC; safety factors applied according to EU guidance

ATTACHMENT 4-1. (continued)

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
298-46-4	Carbamazepine	PNEC	0.42 ug/L	Ferrari et al 2003	Based on chronic NOECs for bacteria, algae, invertebrates and fish; safety factor applied to modeled $HC_{5,50}$ value
333-41-5	Diazinon	Chronic IPS	0.0016 ug/L	Sabo et al. 2008, as cited in Hull et al.2015	Based on chronic value; original document not located on-line
486-56-6	Cotinine	Calc'd PNEC	4747 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (4747 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
525-66-6	Propranolol	PNEC	0.01 ug/L	Ferrari et al 2004	Chronic PNEC based on lowest reference value derived from acute and reproductive toxicity data in algae and ceriodaphnia, and embryo mortality, growth, and reproduction tests in fish; safety factors applied
611-59-6	Dimethylxanthine, 1,7-	Calc'd PNEC	1679 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (1679 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
657-24-9	Metformin	PNEC	130 ug/L	Carlsson et al 2006	Based on lowest among 6 acute ecotoxicity reference values reported in studies in algae, invertebrates, and fish; safety factors applied
657-24-9	Metformin	Calc'd PNEC	0.00033	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish ($3.32x10^{-4}$ mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
723-46-6	Sulfamethoxazole	PNEC	563 ug/L	Ginebreda et al 2009	Acute PNEC derived from a measured acute tox EC50 value for fish, by dividing the EC50 by an "arbitrary" safety factor of 1000
723-46-6	Sulfamethoxazole	PNEC	0.59 ug/L	Ferrari et al 2004	Chronic PNEC based on lowest reference value derived from acute and reproductive toxicity data in algae and ceriodaphnia, and embryo mortality test in fish; safety factors applied
723-46-6	Sulfamethoxazole	PNEC	0.03 ug/L	Park and Choi 2008	Acute PNEC based on lowest reference value reported in acute toxicity studies in bacteria, algae, invertebrates and fish; safety factor of 1000 applied
738-70-5	Trimethoprim	PNEC	795 ug/L	Ginebreda et al 2009; Sanderson et al 2003	Acute PNEC derived from a modeled acute tox EC50 value for fish obtained using the ECOSAR, by dividing the EC50 by an "arbitrary" safety factor of 1000
738-70-5	Trimethoprim	PNEC	0.18 mg/L	Halling-Sorensen et al 2000	Acute PNEC based on lowest reference values for acute toxicity in bacteria, algae, daphnia, and fish; safety factors applied
738-70-5	Trimethoprim	PNEC	60 ug/L	Park and Choi 2008	PNEC based on lowest reference value reported in acute and chronic toxicity studies in algae, invertebrates and fish; safety factor applied

ATTACHMENT 4-1. (continued)

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
1222-05-5	HHCB	PNEC	6.8 ug/L	Balk and Ford 1999; Federle et al (no date)	Based on NOECs in algae, Daphnia, bluegill sunfish and fathead minnow. Only abstract was located; details of derivation were not available.
3380-34-5	Triclosan	PNEC	1550 ng/L	Capdevielle et al 2008	Aquatic organisms (animals, plants, algae); literature review; 14 species; $HC_{5,50}$ of NOECs
3380-34-5	Triclosan	PNEC	115 ng/L	EC/HC 2012, as cited in Hull et al. 2015.	Based on large dataset of ecotoxicity studies in algae, macrophytes, invertebrates, amphibians and fish. Joint publication by Health Canada (HC) and Environment Canada (EC).
15307-79-6	Diclofenac	PNEC	10 ug/L	Carlsson et al 2006	Based on lowest among 18 ecotoxicity reference values reported in studies in bacteria, algae, macrophytes, invertebrates, and fish; safety factors applied
15307-79-6	Diclofenac	PNEC	20 ug/L	Ferrari et al 2004	Chronic PNEC based on lowest reference value derived from acute and reproductive toxicity data in algae and ceriodaphnia, and embryo mortality test in fish; safety factors applied
15307-79-6	Diclofenac	PNEC	0.0001 mg/L	Zhao et al 2010	Based on lowest among 5 measured chronic NOEC; safety factors applied according to EU guidance
15307-79-6	Diclofenac	PNEC	116 ug/L	Ferrari et al 2003	Based on chronic NOECs for bacteria, algae, invertebrates and fish; safety factor applied to modeled $HC_{5,50}$ value
15687-27-1	Ibuprofen	PNEC	7.1 ug/L	Carlsson et al 2006	Based on the second lowest among 8 acute ecotoxicity reference values reported in studies in bacteria, algae, macrophytes, invertebrates, and fish; safety factors applied
15687-27-1	Ibuprofen	PNEC	5 ug/L	Ginebreda et al 2009; Sanderson et al 2003	Acute PNEC derived from a modeled acute tox EC50 value for fish obtained using the ECOSAR, by dividing the EC50 by an "arbitrary" safety factor of 1000
15687-27-1	Ibuprofen	PNEC	0.002 mg/L	Zhao et al 2010	Based on lowest of 2 measured chronic NOEC; safety factors applied according to EU guidance
18559-94-9	Albuterol	Calc'd PNEC	38 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (38 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
20427-84-3	4-Nonylphenol diethoxylate	EQS	30 ng/L	Hansen 2007	EQSs derived from PNECs, which were determined by applying safety factors to NOECs with clear relevance for protecting aquatic communities
21145-77-7	AHTN	PNEC	3.5 ug/L	Balk and Ford 1999	Based on NOECs in algae, Daphnia, bluegill sunfish and fathead minnow. Only abstract was located; details of derivation were not available.

ATTACHMENT 4-1. (continued)

CAS Number(s)	Chemical[26]	Type of Screening Value[27]	Aquatic Toxicity Screening Value (units as reported)	Source	Relevant Methods Elements[28]
37350-58-6; 51384-51-1	Metoprolol	PNEC	944 ug/L	Ginebreda et al 2009	Acute PNEC derived from a measured acute tox EC50 value for fish, by dividing the EC50 by an "arbitrary" safety factor of 1000
37350-58-6; 51384-51-1	Metoprolol	PNEC	8.8 ug/L	Carlsson et al 2006	Based on lowest among 4 acute lethality reference values reported in studies in invertebrates and fish; safety factors applied
37350-58-6; 51384-51-1	Metoprolol	Calc'd PNEC	116 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (116 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
42399-41-7	Diltiazem	Calc'd PNEC	23 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (23 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
49562-28-9	Fenofibrate	Calc'd PNEC	0.8 ug/L	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (0.80 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
51481-61-9	Cimetidine	Calc'd PNEC	571 ug/L	Sanderson et al 2003	Acute PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (571 mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
54910-89-3	Fluotoxine	PNEC	1.7 ug/L	Ginebreda et al 2009; Sanderson et al 2003	Acute PNEC derived from a modeled acute tox EC50 value for fish obtained using the ECOSAR, by dividing the EC50 by an "arbitrary" safety factor of 1000
66357-35-5	Ranitidine	PNEC	1076 ug/L	Ginebreda et al 2009; Sanderson et al 2003	Acute PNEC derived from a modeled acute tox EC50 value for fish obtained using ECOSAR, by dividing the EC50 by an "arbitrary" safety factor of 1000
79617-96-2	Sertraline	PNEC	3.1 ug/L	Styrishave et al 2011	Secondary source, citing Minagh et al 2009.
82419-36-1	Ofloxacin	PNEC	0.5 ug/L	Ferrari et al 2004	Chronic PNEC based on lowest reference value derived from acute and reproductive toxicity data in algae and ceriodaphnia, and embryo mortality test in fish; safety factors applied
85721-33-1	Ciprofloxacin	Calc'd PNEC	0.000025	Sanderson et al 2003	Acute fish PNEC derived by FWS from ECOSAR-modeled acute EC50 value in fish (2.46×10^{-5} mg/L), by applying standard 1000 safety factor per Ginebreda et al 2009
93106-60-6	Enrofloxacin	PNEC	0.049 ug/L	Park and Choi 2008	Acute PNEC based on lowest reference value reported in acute toxicity studies in algae, macrophytes, invertebrates and fish; safety factor of 1000 applied

ATTACHMENT 4-2. Screening value (SV) point estimates for emerging contaminants corresponding to effect concentrations presented in individual records of the CEC Fish Ecotoxicity Database described in Chapter 2.

Attachment 4-2A. Population-relevant SV_{HIGH} Point Estimates (N = 99).

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Androstene-3,17-dione, 4-	Growth	40	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	16.1616	Mosquitofish	juvenile	Stanko	2007
Bisphenol A	Behavioral	1500	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	606.0606	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	1	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.4040	Zebrafish	embryo	WU	2011
Bisphenol A	Developmental	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4.0404	Zebrafish	adult	Keiter	2012
Bisphenol A	Developmental	20	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	8.0808	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	50	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	20.2020	Japanese medaka	larva, juvenile	Metcalfe	2001
Bisphenol A	Developmental	160	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	64.6465	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	80.8081	Japanese medaka	embryo	Pastva	2001
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	80.8081	Japanese medaka	embryo, larva	Sun	2014
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	80.8081	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	80.8081	Ricefish	embryo	Huang	2012
Bisphenol A	Developmental	228	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	92.1212	Zebrafish	embryo	Wang	2013
Bisphenol A	Developmental	355	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	143.4343	Japanese medaka	embryo, larva	YOKOTA	2000
Bisphenol A	Developmental	531	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	214.5455	Fathead minnow	embryo	Sohoni	2001
Bisphenol A	Developmental	1000	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	404.0404	Atlantic salmon	fry	Honkanen	2004
Bisphenol A	Developmental	1000	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	404.0404	Fathead minnow	embryo, larva	WARNER	2007
Bisphenol A	Developmental	1140	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	460.6061	Zebrafish	embryo	McCormick	2010
Bisphenol A	Developmental	2280	Bounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	460.6061	Japanese medaka	adult	Shioda	2000
Bisphenol A	Developmental	1500	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	606.0606	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	6030	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2436.3636	Zebrafish	embryo	Chow	2013

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Growth	640	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	258.5859	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Mortality/ Survival	567	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	229.0909	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Mortality/ Survival	5000	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2020.2020	Guppy	adult	Kinnberg	2003
Bisphenol A	Reproductive	0.43	Unbounded LOAEC	Measured	NA	1	1.5	1.5	1.1	0.1737	Goldfish	adult	Hatef	2012
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.4040	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.4040	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	1.75	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.7071	Brown trout	adult	Lahnsteiner	2005
Bisphenol A	Reproductive	130	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	52.5253	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Reproductive	400	Unbounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	53.8721	Swordtail	adult	KWAK	2001
Bisphenol A	Reproductive	274	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	55.3535	Guppy	adult	Haubruge	2000
Bisphenol A	Reproductive	375	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	151.5152	Zebrafish	embryo to adult	Segner	2003

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Reproductive	837	Unbounded LOAEC	Measured	NA	2	1.5	1.5	1.1	169.0909	Japanese medaka	adult	Kang	2002
Bisphenol A	Reproductive	2280	Bounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	460.6061	Japanese medaka	adult	Shioda	2000
Bisphenol A	Reproductive	5000	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2020.2020	Guppy	adult	Kinnberg	2003
Carbamazepine	Behavioral	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4.0404	Zebrafish	adult	Galus	2014
Carbamazepine	Behavioral	100	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	20.2020	Fathead minnow	juvenile	Thomas	2012
Carbamazepine	Behavioral	1000	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	134.6801	Pumpkinseed sunfish	juvenile	Brandão	2013
Carbamazepine	Behavioral	6150	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	1242.4242	Japanese Medaka	adult	Nassef	2010
Carbamazepine	Behavioral	23600	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	9535.3535	Zebrafish	larva	Ellis	2012
Carbamazepine	Behavioral	94400	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	38141.4141	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Developmental	8.04	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	3.2485	Zebrafish	embryo	Galus	2013
Carbamazepine	Developmental	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4.0404	Zebrafish	adult	Galus	2014
Carbamazepine	Developmental	23600	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	9535.3535	Zebrafish	embryo to juvenile	Lee	2013
Carbamazepine	Developmental	70800	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	28606.0606	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Developmental	122000	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	49292.9293	Zebrafish	embryo	van den Brandhof	2010

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Growth	1780	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	719.1919	Rainbow trout	adult	Li	2009
Carbamazepine	Mortality/ Survival	9890	Bounded LOAEC	Measured	NA	3	1.5	1.5	1.1	1331.9865	Rainbow trout	juvenile	Li	2011
Carbamazepine	Reproductive	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.2020	Zebrafish	adult	Galus	2013
Carbamazepine	Reproductive	1780	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	359.5960	Zebrafish	adult	Madureira	2011
Citalopram	Behavioral	2.3	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	0.4646	Guppy	adult	Olsen	2014
Citalopram	Behavioral	15	Unbounded LOAEC	Measured	NA	2	1.5	1.5	1.1	3.0303	Guppy	adult	Olsen	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Unbounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	16835.0168	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Mortality/ Survival	200000	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	26936.0269	Mosquitofish	adult	Michael	1974
Diphenhydramine	Behavioral	5.6	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	2.2626	Fathead Minnow	larva	Berninger	2011
Diphenhydramine	Developmental	49.1	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	19.8384	Fathead Minnow	larva	Berninger	2011
Estrone	Behavioral	0.05	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.0202	Fathead minnow	embryo	McGee	2009
Estrone	Developmental	0.05	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.0202	Japanese medaka	embryo, larva	Lei	2013

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Estrone	Developmental	0.1	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.0404	Japanese medaka	larva, juvenile	Metcalfe	2001
Estrone	Developmental	0.484	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	0.1956	Java medaka	embryo to adult	Imai	2007
Estrone	Developmental	0.5	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.2020	Japanese medaka	embryo, larva	Lei	2013
Estrone	Reproductive	0.036	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	0.0073	Goldfish	juvenile	Hua	2013
Estrone	Reproductive	0.781	Bounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	0.1578	Fathead minnow	adult	Thorpe	2007
Hexahydro Hexamethyl Cyclopenta benzopyran	Behavioral	182	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	36.7677	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta benzopyran	Developmental	140	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	56.5657	Fathead minnow	egg to larva	Croudace	1997
Hexahydro Hexamethyl Cyclopenta benzopyran	Growth	393	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	79.3939	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta benzopyran	Mortality/ Survival	393	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	79.3939	Bluegill	adult	Wöthrich	1996
Ibuprofen	Developmental	0.1	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.0404	Japanese medaka	egg, embryo, larva, adult (life	Han	2010

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
												cycle test)		
Ibuprofen	Developmental	8.9	Bounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	1.7980	Zebrafish	adult	Ji	2013
Ibuprofen	Mortality/ Survival	1	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.4040	Japanese medaka	egg, embryo, larva, adult (life cycle test)	Han	2010
Ibuprofen	Mortality/ Survival	1000	Bounded LOAEC	Measured	NA	2	1.5	1.5	1.1	202.0202	Zebrafish	adult	Ji	2013
Ibuprofen	Mortality/ Survival	17600	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	2370.3704	Common carp	juvenile	Islas-Flores	2014
Ibuprofen	Reproductive	0.1	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	0.0202	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.4040	Japanese medaka	juvenile, adult	Flippin	2007
Ibuprofen	Reproductive	21	Unbounded LOAEC	Measured	NA	3	1.5	1.5	1.1	2.8283	Zebrafish	adult	Morthorst	2013
Lidocaine	Behavioral	11750	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4747.4747	Zebrafish	larva	Ellis	2012
Sitosterol, beta-	Behavioral	10	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	2.0202	Beta fish	adult	Clotfelter	2006

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Sitosterol, beta-	Behavioral	1000	Bounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	202.0202	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2020.2020	Flagfish	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2020.2020	Japanese medaka	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	2020.2020	Rainbow trout	embryo to juvenile	Orrego	2011
Triclosan	Behavioral	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4.0404	Fathead minnow	larva	Fritsch	2013
Triclosan	Behavioral	71.3	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	28.8081	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Behavioral	170	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	34.3434	Japanese medaka	juvenile	Nassef	2010
Triclosan	Behavioral	500	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	67.3401	Zebrafish	adult	Oliveira	2009
Triclosan	Developmental	71.3	Bounded LOAEC	Measured	NA	1	1.5	1.5	1.1	28.8081	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Developmental	100	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	40.4040	Japanese medaka	larva	Foran	2000
Triclosan	Developmental	313	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	126.4646	Japanese Medaka	embryo	Ishibashi	2004

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Triclosan	Developmental	500	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	202.0202	Zebrafish	embryo	Oliveira	2009
Triclosan	Mortality/ Survival	300	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	40.4040	Zebrafish	adult	Oliveira	2009
Triclosan	Reproductive	101	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	40.8081	Mosquitofish	adult	Raut	2010
Tris(2-butoxyethyl) phosphate	Behavioral	13000	Bounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	1750.8418	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Tris(2-butoxyethyl) phosphate	Developmental	800	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	323.2323	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Developmental	20000	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	8080.8081	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Mortality/ Survival	2800	Unbounded LOAEC	Nominal	NA	3	1.5	1.5	1.1	377.1044	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.2020	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	0.2020	Fathead Minnow	larva	Painter	2009
Venlafaxine	Behavioral	50	Unbounded LOAEC	Nominal	NA	2	1.5	1.5	1.1	10.1010	Fathead minnow	juvenile	Thomas	2012
Venlafaxine	Mortality/ Survival	0.305	Unbounded LOAEC	Measured	NA	2	1.5	1.5	1.1	0.0616	Fathead Minnow	adult	Schultz	2011

ATTACHMENT 4-2a. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{HIGH} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Venlafaxine	Reproductive	10	Bounded LOAEC	Nominal	NA	1	1.5	1.5	1.1	4.0404	Zebrafish	adult	Galus	2013

Attachment 4-2B. Population-relevant SV_{LOW} Point Estimates (N = 167).

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Androstene-3,17-dione, 4-	Growth	4	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0254375	Mosquitofish	juvenile	Stanko	2007
Androstene-3,17-dione, 4-	Reproductive	0.04	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0002544	Mosquitofish	juvenile	Stanko	2007
Androstene-3,17-dione, 4-	Reproductive	0.7	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0022258	Guppy	adult	Hallgren	2009
Bisphenol A	Behavioral	1500	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	3.8156288	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	0.1	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0006359	Zebrafish	embryo	WU	2011
Bisphenol A	Developmental	10	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0254375	Zebrafish	adult	Keiter	2012
Bisphenol A	Developmental	20	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0508751	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	10	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0635938	Japanese medaka	larva, juvenile	Metcalfe	2001
Bisphenol A	Developmental	16	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.1017501	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Developmental	20	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.1271876	Japanese medaka	embryo	Pastva	2001
Bisphenol A	Developmental	60	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.3815629	Japanese medaka	embryo, larva	Sun	2014
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.5087505	Japanese medaka	embryo, larva	Ramakrishnan	2008

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.5087505	Ricefish	embryo	Huang	2012
Bisphenol A	Developmental	228	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.5799756	Zebrafish	embryo	Wang	2013
Bisphenol A	Developmental	48.8	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.6206756	Brown trout	embryo, larva	Bjerregaard	2008
Bisphenol A	Developmental	100	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.6359381	Atlantic salmon	fry	Honkanen	2004
Bisphenol A	Developmental	100	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.6359381	Fathead minnow	embryo, larva	WARNER	2007
Bisphenol A	Developmental	71.2	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.9055759	Japanese medaka	embryo, larva	YOKOTA	2000
Bisphenol A	Developmental	200	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	1.2718763	Japanese medaka	larva	Pastva	2001
Bisphenol A	Developmental	128	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	1.6280016	Fathead minnow	embryo	Sohoni	2001
Bisphenol A	Developmental	684	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	2.1749084	Japanese medaka	adult	Shioda	2000
Bisphenol A	Developmental	375	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	2.3847680	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	1140	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	2.8998779	Zebrafish	embryo	McCormick	2010
Bisphenol A	Developmental	567	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	7.2115385	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Developmental	579	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	7.3641636	Fathead minnow	embryo, larva	Staples	2011
Bisphenol A	Developmental	3120	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	19.8412698	Japanese medaka	adult	Kang	2002
Bisphenol A	Developmental	4020	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	25.5647131	Zebrafish	embryo	Chow	2013
Bisphenol A	Growth	20	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.1271876	Swordtail	juvenile, adult	KWAK	2001

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Growth	49.1	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.1561228	Rare minnow	adult	Zhang	2014
Bisphenol A	Growth	49.1	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.3122456	Rare minnow	adult	Zhang	2014
Bisphenol A	Growth	160	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	1.0175010	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Growth	1000	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	3.1796907	Zebrafish	adult	Molina	2013
Bisphenol A	Growth	1055.4	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	6.7116911	Common carp	juvenile	Mandich	2007
Bisphenol A	Growth	567	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	7.2115385	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Growth	1280	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	8.1400081	Fathead minnow	F1 and F2 juveniles; F0 and F1 adults	Staples	2011
Bisphenol A	Mortality/ Survival	130	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	1.6534392	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Mortality/ Survival	500	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	3.1796907	Guppy	adult	Kinnberg	2003
Bisphenol A	Mortality/ Survival	1000	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	3.1796907	Zebrafish	adult	Molina	2013
Bisphenol A	Mortality/ Survival	1055.4	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	6.7116911	Common carp	juvenile	Mandich	2007
Bisphenol A	Mortality/ Survival	1280	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	8.1400081	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Mortality/ Survival	1280	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	8.1400081	Fathead minnow	F1 and F2 juveniles	Staples	2011
Bisphenol A	Mortality/ Survival	3120	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	19.8412698	Japanese medaka	adult	Kang	2002
Bisphenol A	Reproductive	0.43	Unbounded LOAEC	Measured	3	1	4.8	9.1	1.8	0.0018230	Goldfish	adult	Hatef	2012
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0025438	Fathead minnow	adult	Sohoni	2001

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0025438	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	1.75	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0044516	Brown trout	adult	Lahnsteiner	2005
Bisphenol A	Reproductive	5	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0158985	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	5	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0317969	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	400	Unbounded LOAEC	Nominal	5	3	4.8	9.1	1.8	0.3391670	Swordtail	adult	KWAK	2001
Bisphenol A	Reproductive	274	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.3484941	Guppy	adult	Haubruge	2000
Bisphenol A	Reproductive	94	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.5977818	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Reproductive	52.8	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.6715507	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Reproductive	837	Unbounded LOAEC	Measured	3	2	4.8	9.1	1.8	1.7742674	Japanese medaka	adult	Kang	2002
Bisphenol A	Reproductive	684	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	2.1749084	Japanese medaka	adult	Shioda	2000
Bisphenol A	Reproductive	500	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	3.1796907	Guppy	adult	Kinnberg	2003
Carbamazepine	Behavioral	10	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0254375	Zebrafish	adult	Galus	2014
Carbamazepine	Behavioral	100	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.1271876	Fathead minnow	juvenile	Thomas	2012
Carbamazepine	Behavioral	500	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	1.0598969	Pumpkinseed sunfish	juvenile	Brandão	2013

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Behavioral	6150	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	7.8220391	Japanese Medaka	adult	Nassef	2010
Carbamazepine	Behavioral	23600	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	60.0325600	Zebrafish	larva	Ellis	2012
Carbamazepine	Behavioral	82600	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	525.2849003	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Developmental	0.57	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.0072497	Zebrafish	embryo	Galus	2013
Carbamazepine	Developmental	10	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0254375	Zebrafish	adult	Galus	2014
Carbamazepine	Developmental	862	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	10.9635735	Fathead Minnow	embryo, larva	Overturf	2012
Carbamazepine	Developmental	23600	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	60.0325600	Zebrafish	embryo to juvenile	Lee	2013
Carbamazepine	Developmental	70800	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	180.0976801	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Developmental	61200	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	778.3882784	Zebrafish	embryo	van den Brandhof	2010
Carbamazepine	Growth	180	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	2.2893773	Rainbow trout	adult	Li	2009
Carbamazepine	Growth	1780	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	5.6598494	Zebrafish	adult	Madureira	2012
Carbamazepine	Growth	19900	Unbounded NOAEC	Nominal	2	3	4.8	9.1	1.8	42.1838964	Rainbow trout	juvenile	Li	2011
Carbamazepine	Mortality/ Survival	1780	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	5.6598494	Zebrafish	adult	Madureira	2012
Carbamazepine	Mortality/ Survival	4920	Bounded NOAEC	Measured	1	3	4.8	9.1	1.8	20.8587709	Rainbow trout	juvenile	Li	2011
Carbamazepine	Reproductive	0.5	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0012719	Zebrafish	adult	Galus	2013
Carbamazepine	Reproductive	1780	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	2.2639398	Zebrafish	adult	Madureira	2011
Citalopram	Behavioral	0.2	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0012719	Guppy	adult	Olsen	2014
Citalopram	Behavioral	1	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0031797	Guppy	adult	Olsen	2014
Citalopram	Behavioral	15	Unbounded LOAEC	Measured	3	2	4.8	9.1	1.8	0.0317969	Guppy	adult	Olsen	2014

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Citalopram	Behavioral	100	Unbounded NOAEC	Nominal	2	3	4.8	9.1	1.8	0.2119794	Guppy	adult	Holmberg	2011
Citalopram	Behavioral	100	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.6359381	Rainbow trout	fry	Holmberg	2011
diethyl-meta-toluamide, N,N-	Growth	0.6	Unbounded NOAEC	Measured	1	3	4.8	9.1	1.8	0.0025438	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Growth	1000	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	3.1796907	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	0.6	Unbounded NOAEC	Measured	1	3	4.8	9.1	1.8	0.0025438	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Unbounded LOAEC	Nominal	5	3	4.8	9.1	1.8	105.9896893	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	264.9742233	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Reproductive	0.6	Unbounded NOAEC	Measured	1	3	4.8	9.1	1.8	0.0025438	Fathead minnow	adult	ZENOBIO	2014
Diphenhydramine	Behavioral	2.8	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.0356125	Fathead Minnow	larva	Berninger	2011
Diphenhydramine	Developmental	24.5	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.3116097	Fathead Minnow	larva	Berninger	2011
Estrone	Behavioral	0.005	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0000318	Fathead minnow	embryo	McGee	2009
Estrone	Behavioral	0.1	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0006359	Fathead minnow	larva	McGee	2009
Estrone	Developmental	0.005	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0000318	Japanese medaka	embryo, larva	Lei	2013
Estrone	Developmental	0.01	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0000636	Japanese medaka	larva, juvenile	Metcalfe	2001
Estrone	Developmental	0.05	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0003180	Japanese medaka	embryo, larva	Lei	2013
Estrone	Developmental	0.1	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0006359	Fathead minnow	embryo, larva	McGee	2009

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Estrone	Developmental	0.781	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0024833	Fathead minnow	adult	Thorpe	2007
Estrone	Developmental	0.198	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.0025183	Java medaka	embryo to adult	Imai	2007
Estrone	Mortality/ Survival	0.264	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0016789	Brown trout	juvenile	BJERREGAARD	2008
Estrone	Reproductive	0.016	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0001018	Goldfish	juvenile	Hua	2013
Estrone	Reproductive	0.0993	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0003157	Fathead minnow	adult	Panter	1998
Estrone	Reproductive	0.307	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0009762	Fathead minnow	adult	Thorpe	2007
Estrone	Reproductive	0.494	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0015708	Zebrafish	adult	Van den Belt	2004
Hexahydro hexamethyl cyclopenta benzopyran	Behavioral	93	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.5914225	Bluegill	adult	Wüthrich	1996
Hexahydro hexamethyl cyclopenta benzopyran	Developmental	68	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.8648759	Fathead minnow	egg to larva	Croudace	1997
Hexahydro hexamethyl cyclopenta benzopyran	Developmental	1000	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	6.3593814	Zebrafish	embryo	Carlsson	2004
Hexahydro hexamethyl cyclopenta benzopyran	Growth	182	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	1.1574074	Bluegill	adult	Wüthrich	1996
Hexahydro hexamethyl cyclopenta benzopyran	Mortality/ Survival	182	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	1.1574074	Bluegill	adult	Wüthrich	1996
Ibuprofen	Behavioral	680	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	8.6487586	Fathead Minnow	embryo, larva	Overturf	2012

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Ibuprofen	Developmental	0.01	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0000636	Japanese medaka	life cycle test	Han	2010
Ibuprofen	Developmental	1	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0031797	Zebrafish	adult	Ji	2013
Ibuprofen	Developmental	680	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	8.6487586	Fathead Minnow	embryo, larva	Overturf	2012
Ibuprofen	Growth	8.9	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0282992	Zebrafish	adult	Ji	2013
Ibuprofen	Growth	506	Unbounded NOAEC	Measured	1	3	4.8	9.1	1.8	2.1452313	Zebrafish	adult	Morthorst	2013
Ibuprofen	Mortality/ Survival	0.1	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0006359	Japanese medaka	life cycle test	Han	2010
Ibuprofen	Mortality/ Survival	8.9	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0282992	Zebrafish	adult	Ji	2013
Ibuprofen	Mortality/ Survival	111.2	Bounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.7071632	Zebrafish	adult	Ji	2013
Ibuprofen	Mortality/ Survival	9500	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	20.1380410	Common carp	juvenile	Islas-Flores	2014
Ibuprofen	Reproductive	0.1	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.0001272	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	1	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0025438	Japanese medaka	juvenile, adult	Flippin	2007
Ibuprofen	Reproductive	21	Unbounded LOAEC	Measured	3	3	4.8	9.1	1.8	0.0296771	Zebrafish	adult	Morthorst	2013
Lidocaine	Behavioral	11750	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	29.8890924	Zebrafish	larva	Ellis	2012
Sitosterol, beta-	Behavioral	1	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0031797	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Behavioral	10	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.0127188	Beta fish	adult	Clotfelter	2006
Sitosterol, beta-	Developmental	745	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	9.4754782	Fathead minnow	life-cycle test	FLINDERS	2014
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	12.7187627	Flagfish	embryo to juvenile	Orrego	2011

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	12.7187627	Japanese medaka	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	12.7187627	Rainbow trout	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Growth	150	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.4769536	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Growth	150	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.4769536	Rainbow trout	juvenile	Tremblay	1999
Sitosterol, beta-	Growth	745	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	9.4754782	Fathead minnow	life-cycle test	FLINDERS	2014
Sitosterol, beta-	Mortality/ Survival	1000	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	3.1796907	Beta fish	adult	Clotfelter	2006
Sitosterol, beta-	Reproductive	1	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0031797	Siamese fighting fish	adult	Stevenson	2011
Sitosterol, beta-	Reproductive	1	Unbounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0031797	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Reproductive	10	Bounded NOAEC	Nominal	2	2	4.8	9.1	1.8	0.0317969	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Reproductive	150	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.1907814	Rainbow trout	juvenile	Tremblay	1999
Sitosterol, beta-	Reproductive	745	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	9.4754782	Fathead minnow	life-cycle test	FLINDERS	2014
Triclosan	Behavioral	0.449	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0028554	Fathead minnow	adult	Schultz	2012
Triclosan	Behavioral	0.45	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0028617	Fathead minnow	larva	Schultz	2012
Triclosan	Behavioral	10	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0254375	Fathead minnow	larva	Fritsch	2013
Triclosan	Behavioral	170	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.2162190	Japanese medaka	juvenile	Nassef	2010
Triclosan	Behavioral	34.1	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.4337098	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Behavioral	400	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	0.8479175	Zebrafish	adult	Oliveira	2009

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Triclosan	Developmental	0.45	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0028617	Fathead minnow	larva	Schultz	2012
Triclosan	Developmental	10	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0635938	Japanese medaka	larva	Foran	2000
Triclosan	Developmental	34.1	Bounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.4337098	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Developmental	156	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.9920635	Japanese Medaka	embryo	Ishibashi	2004
Triclosan	Developmental	300	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	1.9078144	Zebrafish	embryo	Oliveira	2009
Triclosan	Growth	0.449	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0028554	Fathead minnow	adult	Schultz	2012
Triclosan	Growth	101	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.6422975	Mosquitofish	adult	Raut	2010
Triclosan	Growth	136.9	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.8705993	Japanese Medaka	adult	Ishibashi	2004
Triclosan	Mortality/ Survival	0.449	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0028554	Fathead minnow	adult	Schultz	2012
Triclosan	Mortality/ Survival	200	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	0.4239588	Zebrafish	adult	Oliveira	2009
Triclosan	Reproductive	0.449	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0028554	Fathead minnow	adult	Schultz	2012
Triclosan	Reproductive	58	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.3688441	Mosquitofish	adult	Raut	2010
Triclosan	Reproductive	136.9	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.8705993	Japanese Medaka	adult	Ishibashi	2004
Tris (2-butoxyethyl) phosphate	Behavioral	7800	Bounded NOAEC	Nominal	2	3	4.8	9.1	1.8	16.5343915	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Tris (2-butoxyethyl) phosphate	Developmental	150	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.9539072	Zebrafish	embryo	Han	2014

Attachment 4-2B. (continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L)	Type of Effect Concentration	Type of Reported Exposure Concentration	UF_{Conc} (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Population-relevant SV_{LOW} - Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Tris (2-butoxyethyl) phosphate	Developmental	4000	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	25.4375254	Zebrafish	embryo	Han	2014
Tris (2-butoxyethyl) phosphate	Mortality/ Survival	2800	Unbounded LOAEC	Nominal	5	3	4.8	9.1	1.8	2.3741690	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0012719	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	5	1	4.8	9.1	1.8	0.0012719	Fathead Minnow	larva	Painter	2009
Venlafaxine	Behavioral	50	Unbounded LOAEC	Nominal	5	2	4.8	9.1	1.8	0.0635938	Fathead minnow	juvenile	Thomas	2012
Venlafaxine	Developmental	5	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0317969	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Developmental	5	Unbounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0317969	Fathead Minnow	larva	Painter	2009
Venlafaxine	Developmental	4.35	Unbounded NOAEC	Measured	1	1	4.8	9.1	1.8	0.0553266	Zebrafish	embryo	Galus	2013
Venlafaxine	Growth	1.104	Unbounded NOAEC	Measured	1	2	4.8	9.1	1.8	0.0070208	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Mortality/ Survival	0.305	Unbounded LOAEC	Measured	3	2	4.8	9.1	1.8	0.0006465	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	0.305	Unbounded LOAEC	Measured	3	2	4.8	9.1	1.8	0.0006465	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	0.5	Bounded NOAEC	Nominal	2	1	4.8	9.1	1.8	0.0031797	Zebrafish	adult	Galus	2013

Attachment 4-2C. Comprehensive SV_{HIGH} Point Estimates (N = 141).

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Androstene-3,17-dione, 4-	Growth	40	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	15.1515	Mosquitofish	juvenile	Stanko	2007
Androstene-3,17-dione, 4-	Reproductive	50	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	9.4697	Guppy	adult	Hallgren	2009
Androstene-3,17-dione, 4-	Reproductive	0.4	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1515	Mosquitofish	juvenile	Stanko	2007
Bisphenol A	Behavioral	1500	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	568.1818	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	1000	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	378.7879	Atlantic salmon	fry	Honkanen	2004
Bisphenol A	Developmental	531	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	201.1364	Fathead minnow	embryo	Sohoni	2001
Bisphenol A	Developmental	1000	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	378.7879	Fathead minnow	embryo, larva	Warner	2007
Bisphenol A	Developmental	20	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	7.5758	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	50	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	18.9394	Japanese medaka	larva, juvenile	Metcalfe	2001
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo	Pastva	2001

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	50	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	18.9394	Japanese medaka	larva, juvenile	Metcalfe	2001
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo	Pastva	2001
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo, larva	Sun	2014
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	355	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	134.4697	Japanese medaka	embryo, larva	YOKOTA	2000
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Ricefish	embryo	Huang	2012
Bisphenol A	Developmental	0.1	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0379	Zebrafish	embryo	Xu	2013
Bisphenol A	Developmental	1	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Zebrafish	embryo	WU	2011
Bisphenol A	Developmental	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Zebrafish	adult	Keiter	2012
Bisphenol A	Developmental	228	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	86.3636	Zebrafish	embryo	Wang	2013

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Reproductive	375	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	142.0455	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	1500	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	568.1818	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	800	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	303.0303	Zebrafish	larva	Chan	2012
Bisphenol A	Developmental	1140	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	431.8182	Zebrafish	embryo	McCormick	2010
Bisphenol A	Developmental	6030	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	2284.0909	Zebrafish	embryo	Chow	2013
Bisphenol A	Gross Pathology	130	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	49.2424	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Growth	640	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	242.4242	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Mortality/ Survival	567	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	214.7727	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Mortality/ Survival	5000	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	1893.9394	Guppy	adult	Kinnberg	2003
Bisphenol A	Reproductive	1.75	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.6629	Brown trout	adult	Lahnsteiner	2005

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Reproductive	0.85	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.1610	Common carp	juvenile	Mandich	2007
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Developmental	160	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	60.6061	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	130	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	49.2424	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Reproductive	0.43	Unbounded LOAEC	Measured	NA	1	1.5	1.6	1.1	0.1629	Goldfish	adult	Hatef	2012
Bisphenol A	Reproductive	274	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	51.8939	Guppy	adult	Haubruge	2000
Bisphenol A	Reproductive	5000	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	1893.9394	Guppy	adult	Kinnberg	2003
Bisphenol A	Reproductive	837	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	158.5227	Japanese medaka	adult	Kang	2002
Bisphenol A	Reproductive	2280	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	431.8182	Japanese medaka	adult	Shioda	2000

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	2280	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	431.8182	Japanese medaka	adult	Shioda	2000
Bisphenol A	Reproductive	15	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	2.8409	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	15	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	5.6818	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	400	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	50.5051	Swordtail	adult	KWAK	2001
Bisphenol A	Reproductive	100	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	18.9394	Zebrafish	adult	Molina	2013
Carbamazepine	Behavioral	100	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	18.9394	Fathead minnow	juvenile	Thomas	2012
Carbamazepine	Behavioral	6150	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	1164.7727	Japanese Medaka	adult	Nassef	2010
Carbamazepine	Behavioral	1000	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	126.2626	Pumpkinseed sunfish	juvenile	Brandão	2013
Carbamazepine	Behavioral	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Zebrafish	adult	Galus	2014
Carbamazepine	Behavioral	23600	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	8939.3939	Zebrafish	larva	Ellis	2012

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Behavioral	94400	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	35757.5758	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Circulatory/ Blood Constituents	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Rainbow trout	adult	Li	2010
Carbamazepine	Circulatory/ Blood Constituents	19900	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	2512.6263	Rainbow trout	juvenile	Li	2011
Carbamazepine	Developmental	8.04	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	3.0455	Zebrafish	embryo	Galus	2013
Carbamazepine	Developmental	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Zebrafish	adult	Galus	2014
Carbamazepine	Developmental	23600	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	8939.3939	Zebrafish	embryo to juvenile	Lee	2013
Carbamazepine	Developmental	70800	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	26818.1818	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Developmental	122000	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	46212.1212	Zebrafish	embryo	van den Brandhof	2010
Carbamazepine	Growth	1780	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	674.2424	Rainbow trout	adult	Li	2009
Carbamazepine	Histopathology	1	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	0.1894	Common carp	juvenile	Triebskorn	2007

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Histopathology	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Zebrafish	adult	Galus	2013
Carbamazepine	Mortality /Survival	9890	Bounded LOAEC	Measured	NA	3	1.5	1.6	1.1	1248.7374	Rainbow trout	juvenile	Li	2011
Carbamazepine	Neurological	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Rainbow trout	adult	Li	2010
Carbamazepine	Neurological	19900	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	2512.6263	Rainbow trout	juvenile	Li	2011
Carbamazepine	Physiology/ Metabolism	180	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	68.1818	Rainbow trout	adult	Li	2010
Carbamazepine	Physiology/ Metabolism	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Rainbow trout	adult	Li	2010
Carbamazepine	Physiology/ Metabolism	1780	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	674.2424	Rainbow trout	adult	Li	2009
Carbamazepine	Physiology/ Metabolism	19900	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	2512.6263	Rainbow trout	juvenile	Li	2011
Carbamazepine	Reproductive	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Zebrafish	adult	Galus	2013
Carbamazepine	Reproductive	1780	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	337.1212	Zebrafish	adult	Madureira	2011

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Citalopram	Behavioral	2.3	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.4356	Guppy	adult	Olsen	2014
Citalopram	Behavioral	15	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	2.8409	Guppy	adult	Olsen	2014
diethyl-meta-toluamide, N,N-	Circulatory/ Blood Constituents	1000	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	189.3939	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Endocrine/ Hormone	0.6	Unbounded LOAEC	Measured	NA	3	1.5	1.6	1.1	0.0758	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	15782.8283	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Mortality/ Survival	200000	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	25252.5253	Mosquitofish	adult	Michael	1974
Diphenhydramine	Behavioral	5.6	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	2.1212	Fathead Minnow	larva	Berninger	2011
Diphenhydramine	Developmental	49.1	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	18.5985	Fathead Minnow	larva	Berninger	2011
Estrone	Behavioral	0.05	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0189	Fathead minnow	embryo	McGee	2009
Estrone	Developmental	0.05	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0189	Japanese medaka	embryo, larva	Lei	2013

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Estrone	Developmental	0.1	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0379	Japanese medaka	larva, juvenile	Metcalfe	2001
Estrone	Developmental	0.5	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Japanese medaka	embryo, larva	Lei	2013
Estrone	Developmental	0.484	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	0.1833	Java medaka	embryo to adult	Imai	2007
Estrone	Physiology /Metabolism	0.0027	Bounded LOAEC	Nominal	NA	5	1.5	1.6	1.1	0.0002	Round goby	adult	Belanger	2007
Estrone	Physiology/ Metabolism	0.27	Bounded LOAEC	Nominal	NA	5	1.5	1.6	1.1	0.0205	Round goby	juvenile	Belanger	2007
Estrone	Reproductive	0.3177	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	0.0602	Fathead minnow	adult	Panter	1998
Estrone	Reproductive	0.781	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	0.1479	Fathead minnow	adult	Thorpe	2007
Estrone	Reproductive	0.036	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.0068	Goldfish	juvenile	Hua	2013
Estrone	Reproductive	0.988	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	0.1871	Zebrafish	adult	Van den Belt	2004
Hexahydro Hexamethyl Cyclopenta Benzopyran	Behavioral	182	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	34.4697	Bluegill	adult	Wüthrich	1996

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Hexahydro Hexamethyl Cyclopenta Benzopyran	Developmental	140	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	53.0303	Fathead minnow	egg to larva	Croudace	1997
Hexahydro Hexamethyl Cyclopenta Benzopyran	Growth	393	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	74.4318	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta Benzopyran	Mortality /Survival	393	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	74.4318	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta Benzopyran	Physiology/ Metabolism	15	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	2.8409	Goldfish	adult	Chen	2012
Hexahydro Hexamethyl Cyclopenta Benzopyran	Reproductive	25.8	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	3.2576	Zebrafish	juvenile	Schreurs	2004
Ibuprofen	Circulatory/ Blood Constituents	14200	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	5378.7879	Indian major carp	juvenile	Saravanan	2012
Ibuprofen	Developmental	0.1	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0379	Japanese medaka	egg, embryo, larva, adult (life cycle test)	Han	2010
Ibuprofen	Developmental	8.9	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	1.6856	Zebrafish	adult	Ji	2013
Ibuprofen	Endocrine/ Hormone	1000	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	189.3939	Rainbow trout	juvenile	Gravel	2009

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Ibuprofen	Genotoxicity	0.0664	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.0126	Zebrafish	adult	Rocco	2010
Ibuprofen	Mortality/ Survival	17600	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	2222.2222	Common carp	juvenile	Islas-Flores	2014
Ibuprofen	Mortality/ Survival	1	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Japanese medaka	egg, embryo, larva, adult (life cycle test)	Han	2010
Ibuprofen	Mortality/ Survival	1000	Bounded LOAEC	Measured	NA	2	1.5	1.6	1.1	189.3939	Zebrafish	adult	Ji	2013
Ibuprofen	Physiology/ Metabolism	1000	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	189.3939	Rainbow trout	juvenile	Gravel	2009
Ibuprofen	Reproductive	1	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Japanese medaka	juvenile, adult	Flippin	2007
Ibuprofen	Reproductive	0.1	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	0.0189	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	8.6	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	1.6288	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	21	Unbounded LOAEC	Measured	NA	3	1.5	1.6	1.1	2.6515	Zebrafish	adult	Morthorst	2013

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Lidocaine	Behavioral	11750	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	4450.7576	Zebrafish	larva	Ellis	2012
Sitosterol, beta-	Behavioral	10	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	1.8939	Beta fish	adult	Clotfelter	2006
Sitosterol, beta-	Behavioral	1000	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	189.3939	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Circulatory/ Blood Constituents	75	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	14.2045	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Circulatory/ Blood Constituents	75	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	14.2045	Rainbow trout	juvenile	Tremblay	1999
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	1893.9394	Flagfish	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	1893.9394	Japanese medaka	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	1893.9394	Rainbow trout	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Reproductive	75	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	14.2045	Goldfish	adult	MacLatchy	1997
Sitosterol, beta-	Reproductive	300	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	56.8182	Goldfish	adult	MacLatchy	1997

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Sitosterol, beta-	Reproductive	25	Bounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	4.7348	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Reproductive	150	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	28.4091	Rainbow trout	juvenile	Tremblay	1999
Triclosan	Behavioral	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Fathead minnow	larva	Fritsch	2013
Triclosan	Behavioral	170	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	32.1970	Japanese medaka	juvenile	Nassef	2010
Triclosan	Behavioral	71.3	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	27.0076	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Behavioral	500	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	63.1313	Zebrafish	adult	Oliveira	2009
Triclosan	Developmental	100	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	37.8788	Japanese medaka	larva	Foran	2000
Triclosan	Developmental	313	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	118.5606	Japanese Medaka	embryo	Ishibashi	2004
Triclosan	Developmental	71.3	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	27.0076	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Developmental	500	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	189.3939	Zebrafish	embryo	Oliveira	2009

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Triclosan	Mortality/ Survival	300	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	37.8788	Zebrafish	adult	Oliveira	2009
Triclosan	Reproductive	101	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	38.2576	Mosquitofish	adult	Raut	2010
Tris(2-butoxyethyl) phosphate	Behavioral	13000	Bounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	1641.4141	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Tris(2-butoxyethyl) phosphate	Developmental	800	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	303.0303	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Developmental	800	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	303.0303	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Developmental	20000	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	7575.7576	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Mortality/ Survival	2800	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	353.5354	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Fathead Minnow	larva	Painter	2009

Attachment 4-2C. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Venlafaxine	Behavioral	50	Unbounded LOAEC	Nominal	NA	2	1.5	1.6	1.1	9.4697	Fathead minnow	juvenile	Thomas	2012
Venlafaxine	Endocrine/ Hormone	0.2	Unbounded LOAEC	Nominal	NA	3	1.5	1.6	1.1	0.0253	Rainbow trout	juvenile	Best	2014
Venlafaxine	Histopathology	0.5	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.1894	Zebrafish	adult	Galus	2013
Venlafaxine	Mortality/ Survival	0.305	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.0578	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	0.305	Unbounded LOAEC	Measured	NA	2	1.5	1.6	1.1	0.0578	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	10	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Zebrafish	adult	Galus	2013

Attachment 4-2D. Comprehensive SV_{LOW} Point Estimates (N = 214).

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SV_{HIGH} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	200	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo, larva	Sun	2014
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	355	Bounded LOAEC	Measured	NA	1	1.5	1.6	1.1	134.4697	Japanese medaka	embryo, larva	Yokota	2000
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	75.7576	Ricefish	embryo	Huang	2012
Bisphenol A	Developmental	0.1	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.0379	Zebrafish	embryo	Xu	2013
Bisphenol A	Developmental	1	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	0.3788	Zebrafish	embryo	WU	2011
Bisphenol A	Developmental	10	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	3.7879	Zebrafish	adult	Keiter	2012
Bisphenol A	Developmental	228	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	86.3636	Zebrafish	embryo	Wang	2013
Bisphenol A	Reproductive	375	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	142.0455	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	1500	Bounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	568.1818	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	800	Unbounded LOAEC	Nominal	NA	1	1.5	1.6	1.1	303.0303	Zebrafish	larva	Chan	2012

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	20	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0204290	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	10	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0255363	Japanese medaka	larva, juvenile	Metcalfe	2001
Bisphenol A	Developmental	20	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0510725	Japanese medaka	embryo	Pastva	2001
Bisphenol A	Developmental	60	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.1532176	Japanese medaka	embryo, larva	Sun	2014
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.2042901	Japanese medaka	embryo, larva	Ramakrishnan	2008
Bisphenol A	Developmental	71.2	Bounded NOAEC	Measured	1	1	8.9	11	2	0.3636364	Japanese medaka	embryo, larva	YOKOTA	2000
Bisphenol A	Developmental	200	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.5107252	Japanese medaka	larva	Pastva	2001
Bisphenol A	Developmental	3120	Unbounded NOAEC	Measured	1	2	8.9	11	2	7.9673136	Japanese medaka	adult	Kang	2002
Bisphenol A	Developmental	200	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.2042901	Ricefish	embryo	Huang	2012
Bisphenol A	Developmental	0.1	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0001021	Zebrafish	embryo	Xu	2013
Bisphenol A	Developmental	0.1	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0002554	Zebrafish	embryo	WU	2011

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Developmental	10	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0102145	Zebrafish	adult	Keiter	2012
Bisphenol A	Developmental	228	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.2328907	Zebrafish	embryo	Wang	2013
Bisphenol A	Reproductive	94	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.2400409	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	375	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.9576098	Zebrafish	embryo to adult	Segner	2003
Bisphenol A	Developmental	800	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.8171604	Zebrafish	larva	Chan	2012
Bisphenol A	Developmental	1140	Unbounded LOAEC	Nominal	5	1	8.9	11	2	1.1644535	Zebrafish	embryo	McCormick	2010
Bisphenol A	Developmental	4020	Bounded NOAEC	Nominal	2	1	8.9	11	2	10.2655771	Zebrafish	embryo	Chow	2013
Bisphenol A	Developmental	3930	Unbounded NOAEC	Nominal	2	1	8.9	11	2	10.0357508	Zebrafish	embryo	Chan	2012
Bisphenol A	Gross Pathology	52.8	Bounded NOAEC	Measured	1	1	8.9	11	2	0.2696629	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Gross Pathology	3120	Unbounded NOAEC	Measured	1	2	8.9	11	2	7.9673136	Japanese medaka	adult	Kang	2002
Bisphenol A	Growth	1055.4	Unbounded NOAEC	Measured	1	2	8.9	11	2	2.6950970	Common carp	juvenile	Mandich	2007

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Growth	160	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.4085802	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Growth	567	Unbounded NOAEC	Measured	1	1	8.9	11	2	2.8958121	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Growth	1280	Unbounded NOAEC	Nominal	2	1	8.9	11	2	3.2686415	Fathead minnow	F1 and F2 juveniles; F0 and F1 adults	Staples	2011
Bisphenol A	Growth	49.1	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0626915	Rare minnow	adult	Zhang	2014
Bisphenol A	Growth	49.1	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.1253830	Rare minnow	adult	Zhang	2014
Bisphenol A	Growth	20	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0510725	Swordtail	juvenile, adult	KWAK	2001
Bisphenol A	Growth	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Zebrafish	adult	Molina	2013
Bisphenol A	Mortality/ Survival	1055.4	Unbounded NOAEC	Measured	1	2	8.9	11	2	2.6950970	Common carp	juvenile	Mandich	2007
Bisphenol A	Mortality/ Survival	130	Bounded NOAEC	Measured	1	1	8.9	11	2	0.6639428	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Mortality/ Survival	1280	Unbounded NOAEC	Nominal	2	1	8.9	11	2	3.2686415	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Mortality/ Survival	1280	Unbounded NOAEC	Nominal	2	1	8.9	11	2	3.2686415	Fathead minnow	F1 and F2 juveniles	Staples	2011

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Mortality/ Survival	500	Bounded NOAEC	Nominal	2	1	8.9	11	2	1.2768131	Guppy	adult	Kinnberg	2003
Bisphenol A	Mortality/ Survival	3120	Unbounded NOAEC	Measured	1	2	8.9	11	2	7.9673136	Japanese medaka	adult	Kang	2002
Bisphenol A	Mortality/ Survival	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Zebrafish	adult	Molina	2013
Bisphenol A	Reproductive	1.75	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0017875	Brown trout	adult	Lahnsteiner	2005
Bisphenol A	Reproductive	0.85	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0007235	Common carp	juvenile	Mandich	2007
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0010215	Fathead minnow	adult	Sohoni	2001
Bisphenol A	Developmental	16	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0408580	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	1	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0010215	Fathead minnow	F0 and F1 adults; F1 juveniles	Staples	2011
Bisphenol A	Reproductive	52.8	Bounded NOAEC	Measured	1	1	8.9	11	2	0.2696629	Fathead minnow	adult	MIHAICH	2012
Bisphenol A	Reproductive	0.43	Unbounded LOAEC	Measured	3	1	8.9	11	2	0.0007320	Goldfish	adult	Hatef	2012
Bisphenol A	Reproductive	274	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.1399387	Guppy	adult	Haubruge	2000

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Bisphenol A	Reproductive	500	Bounded NOAEC	Nominal	2	1	8.9	11	2	1.2768131	Guppy	adult	Kinnberg	2003
Bisphenol A	Reproductive	837	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.7124617	Japanese medaka	adult	Kang	2002
Bisphenol A	Reproductive	684	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.8733401	Japanese medaka	adult	Shioda	2000
Bisphenol A	Developmental	684	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.8733401	Japanese medaka	adult	Shioda	2000
Bisphenol A	Reproductive	5	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0063841	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	5	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0127681	Rare minnow	adult	Zhang	2014
Bisphenol A	Reproductive	400	Unbounded LOAEC	Nominal	5	3	8.9	11	2	0.1361934	Swordtail	adult	KWAK	2001
Bisphenol A	Reproductive	10	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0127681	Zebrafish	adult	Molina	2013
Carbamazepine	Behavioral	100	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0510725	Fathead minnow	juvenile	Thomas	2012
Carbamazepine	Behavioral	862	Unbounded NOAEC	Measured	1	1	8.9	11	2	4.4024515	Fathead Minnow	embryo, larva	Overturf	2012
Carbamazepine	Behavioral	6150	Unbounded LOAEC	Nominal	5	2	8.9	11	2	3.1409602	Japanese Medaka	adult	Nassef	2010

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Behavioral	500	Bounded NOAEC	Nominal	2	3	8.9	11	2	0.4256044	Pumpkinseed sunfish	juvenile	Brandão	2013
Carbamazepine	Behavioral	10	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0102145	Zebrafish	adult	Galus	2014
Carbamazepine	Behavioral	23600	Unbounded LOAEC	Nominal	5	1	8.9	11	2	24.1062308	Zebrafish	larva	Ellis	2012
Carbamazepine	Behavioral	82600	Bounded NOAEC	Nominal	2	1	8.9	11	2	210.9295199	Zebrafish	embryo	Pruvot	2012
Carbamazepine	Circulatory/ Blood Constituents	1	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0025536	Rainbow trout	adult	Li	2010
Carbamazepine	Circulatory/ Blood Constituents	19900	Unbounded LOAEC	Nominal	5	3	8.9	11	2	6.7756214	Rainbow trout	juvenile	Li	2011
Carbamazepine	Developmental	862	Unbounded NOAEC	Measured	1	1	8.9	11	2	4.4024515	Fathead Minnow	embryo, larva	Overturf	2012
Carbamazepine	Developmental	0.57	Bounded NOAEC	Measured	1	1	8.9	11	2	0.0029111	Zebrafish	embryo	Galus	2013
Carbamazepine	Developmental	10	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0102145	Zebrafish	adult	Galus	2014
Carbamazepine	Developmental	23600	Unbounded LOAEC	Nominal	5	1	8.9	11	2	24.1062308	Zebrafish	embryo to juvenile	Lee	2013
Carbamazepine	Developmental	70800	Unbounded LOAEC	Nominal	5	1	8.9	11	2	72.3186925	Zebrafish	embryo	Pruvot	2012

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Developmental	61200	Bounded NOAEC	Measured	1	1	8.9	11	2	312.5638407	Zebrafish	embryo	van den Brandhof	2010
Carbamazepine	Growth	180	Bounded NOAEC	Measured	1	1	8.9	11	2	0.9193054	Rainbow trout	adult	Li	2009
Carbamazepine	Growth	19900	Unbounded NOAEC	Nominal	2	3	8.9	11	2	16.9390535	Rainbow trout	juvenile	Li	2011
Carbamazepine	Growth	1780	Unbounded NOAEC	Nominal	2	2	8.9	11	2	2.2727273	Zebrafish	adult	Madureira	2012
Carbamazepine	Histopathology	1	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0005107	Common carp	juvenile	Triebskorn	2007
Carbamazepine	Histopathology	0.5	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0005107	Zebrafish	adult	Galus	2013
Carbamazepine	Mortality/ Survival	4920	Bounded NOAEC	Measured	1	3	8.9	11	2	8.3758938	Rainbow trout	juvenile	Li	2011
Carbamazepine	Mortality/ Survival	1780	Unbounded NOAEC	Nominal	2	2	8.9	11	2	2.2727273	Zebrafish	adult	Madureira	2012
Carbamazepine	Neurological	1	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0025536	Rainbow trout	adult	Li	2010
Carbamazepine	Neurological	19900	Unbounded LOAEC	Nominal	5	3	8.9	11	2	6.7756214	Rainbow trout	juvenile	Li	2011
Carbamazepine	Physiology /Metabolism	0.89	Bounded NOAEC	Measured	1	1	8.9	11	2	0.0045455	Rainbow trout	adult	Li	2010

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Carbamazepine	Physiology /Metabolism	1	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0025536	Rainbow trout	adult	Li	2010
Carbamazepine	Physiology /Metabolism	180	Bounded NOAEC	Measured	1	1	8.9	11	2	0.9193054	Rainbow trout	adult	Li	2009
Carbamazepine	Physiology/ Metabolism	19900	Unbounded LOAEC	Nominal	5	3	8.9	11	2	6.7756214	Rainbow trout	juvenile	Li	2011
Carbamazepine	Reproductive	0.5	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0005107	Zebrafish	adult	Galus	2013
Carbamazepine	Reproductive	1780	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.9090909	Zebrafish	adult	Madureira	2011
Citalopram	Behavioral	0.2	Bounded NOAEC	Measured	1	2	8.9	11	2	0.0005107	Guppy	adult	Olsen	2014
Citalopram	Behavioral	15	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0127681	Guppy	adult	Olsen	2014
Citalopram	Behavioral	1	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0012768	Guppy	adult	Olsen	2014
Citalopram	Behavioral	100	Unbounded NOAEC	Nominal	2	3	8.9	11	2	0.0851209	Guppy	adult	Holmberg	2011
Citalopram	Behavioral	100	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.2553626	Rainbow trout	fry	Holmberg	2011
diethyl-meta-toluamide, N,N-	Circulatory/ Blood Constituents	100	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.1276813	Common carp	adult	Slaninova	2014

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
diethyl-meta-toluamide, N,N-	Endocrine/ Hormone	0.6	Unbounded LOAEC	Measured	3	3	8.9	11	2	0.0003405	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Growth	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Growth	0.6	Unbounded NOAEC	Measured	1	3	8.9	11	2	0.0010215	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Histopathology	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Immunological	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	0.6	Unbounded NOAEC	Measured	1	3	8.9	11	2	0.0010215	Fathead minnow	adult	ZENOBIO	2014
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Unbounded LOAEC	Nominal	5	3	8.9	11	2	42.5604358	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Mortality/ Survival	125000	Bounded NOAEC	Nominal	2	3	8.9	11	2	106.4010895	Mosquitofish	adult	Michael	1974
diethyl-meta-toluamide, N,N-	Physiology/ Metabolism	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Common carp	adult	Slaninova	2014
diethyl-meta-toluamide, N,N-	Reproductive	0.6	Unbounded NOAEC	Measured	1	3	8.9	11	2	0.0010215	Fathead minnow	adult	ZENOBIO	2014
Diphenhydramine	Behavioral	2.8	Bounded NOAEC	Measured	1	1	8.9	11	2	0.0143003	Fathead Minnow	larva	Berninger	2011

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Diphenhydramine	Developmental	24.5	Bounded NOAEC	Measured	1	1	8.9	11	2	0.1251277	Fathead Minnow	larva	Berninger	2011
Estrone	Behavioral	0.005	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0000128	Fathead minnow	embryo	McGee	2009
Estrone	Behavioral	0.1	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0002554	Fathead minnow	larva	McGee	2009
Estrone	Developmental	0.1	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0002554	Fathead minnow	embryo, larva	McGee	2009
Estrone	Developmental	0.781	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0009972	Fathead minnow	adult	Thorpe	2007
Estrone	Developmental	0.005	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0000128	Japanese medaka	embryo, larva	Lei	2013
Estrone	Developmental	0.01	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0000255	Japanese medaka	larva, juvenile	Metcalfe	2001
Estrone	Developmental	0.05	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0001277	Japanese medaka	embryo, larva	Lei	2013
Estrone	Developmental	0.198	Bounded NOAEC	Measured	1	1	8.9	11	2	0.0010112	Java medaka	embryo to adult	Imai	2007
Estrone	Mortality/ Survival	0.264	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0006742	Brown trout	juvenile	BJERREGAARD	2008
Estrone	Physiology/ Metabolism	0.00027	Bounded NOAEC	Nominal	2	5	8.9	11	2	0.0000001	Round goby	adult	Belanger	2007

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Estrone	Physiology/ Metabolism	0.027	Bounded NOAEC	Nominal	2	5	8.9	11	2	0.0000138	Round goby	juvenile	Belanger	2007
Estrone	Reproductive	0.0993	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0001268	Fathead minnow	adult	Panter	1998
Estrone	Reproductive	0.307	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0003920	Fathead minnow	adult	Thorpe	2007
Estrone	Reproductive	0.016	Bounded NOAEC	Measured	1	2	8.9	11	2	0.0000409	Goldfish	juvenile	Hua	2013
Estrone	Reproductive	0.494	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0006307	Zebrafish	adult	Van den Belt	2004
Hexahydro Hexamethyl Cyclopenta Benzopyran	Behavioral	93	Bounded NOAEC	Measured	1	2	8.9	11	2	0.2374872	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta Benzopyran	Developmental	68	Bounded NOAEC	Measured	1	1	8.9	11	2	0.3472932	Fathead minnow	egg to larva	Croudace	1997
Hexahydro Hexamethyl Cyclopenta Benzopyran	Developmental	1000	Unbounded NOAEC	Nominal	2	1	8.9	11	2	2.5536261	Zebrafish	embryo	Carlsson	2004
Hexahydro Hexamethyl Cyclopenta Benzopyran	Growth	182	Bounded NOAEC	Measured	1	2	8.9	11	2	0.4647600	Bluegill	adult	Wöthrich	1996
Hexahydro Hexamethyl Cyclopenta Benzopyran	Mortality/ Survival	182	Bounded NOAEC	Measured	1	2	8.9	11	2	0.4647600	Bluegill	adult	Wöthrich	1996

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Hexahydro Hexamethyl Cyclopenta Benzopyran	Physiology/Metabolism	1.5	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0019152	Goldfish	adult	Chen	2012
Hexahydro Hexamethyl Cyclopenta Benzopyran	Reproductive	2.58	Bounded NOAEC	Nominal	2	3	8.9	11	2	0.0021961	Zebrafish	juvenile	Schreurs	2004
Ibuprofen	Behavioral	680	Unbounded NOAEC	Measured	1	1	8.9	11	2	3.4729316	Fathead Minnow	embryo, larva	Overturf	2012
Ibuprofen	Circulatory/ Blood Constituents	14200	Unbounded LOAEC	Nominal	5	1	8.9	11	2	14.5045965	Indian major carp	juvenile	Saravanan	2012
Ibuprofen	Developmental	680	Unbounded NOAEC	Measured	1	1	8.9	11	2	3.4729316	Fathead Minnow	embryo, larva	Overturf	2012
Ibuprofen	Developmental	0.01	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0000255	Japanese medaka	egg, embryo, larva, adult (life cycle test)	Han	2010
Ibuprofen	Developmental	1	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0012768	Zebrafish	adult	Ji	2013
Ibuprofen	Endocrine/Hormone	1000	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.5107252	Rainbow trout	juvenile	Gravel	2009
Ibuprofen	Genotoxicity	0.0664	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0000565	Zebrafish	adult	Rocco	2010
Ibuprofen	Growth	8.9	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0113636	Zebrafish	adult	Ji	2013

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Ibuprofen	Growth	506	Unbounded NOAEC	Measured	1	3	8.9	11	2	0.8614232	Zebrafish	adult	Morthorst	2013
Ibuprofen	Histopathology	100	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.2553626	Japanese medaka	juvenile, adult	Flippin	2007
Ibuprofen	Mortality/ Survival	9500	Bounded NOAEC	Nominal	2	3	8.9	11	2	8.0864828	Common carp	juvenile	Islas-Flores	2014
Ibuprofen	Mortality/ Survival	0.1	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0002554	Japanese medaka	egg, embryo, larva, adult (life cycle test)	Han	2010
Ibuprofen	Mortality/ Survival	111.2	Bounded NOAEC	Measured	1	2	8.9	11	2	0.2839632	Zebrafish	adult	Ji	2013
Ibuprofen	Mortality/ Survival	8.9	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0113636	Zebrafish	adult	Ji	2013
Ibuprofen	Physiology/ Metabolism	1000	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.5107252	Rainbow trout	juvenile	Gravel	2009
Ibuprofen	Reproductive	1	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0010215	Japanese medaka	juvenile, adult	Flippin	2007
Ibuprofen	Reproductive	0.1	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0000511	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	8.6	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0073204	Zebrafish	adult	Ji	2013
Ibuprofen	Reproductive	21	Unbounded LOAEC	Measured	3	3	8.9	11	2	0.0119169	Zebrafish	adult	Morthorst	2013

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Lidocaine	Behavioral	11750	Unbounded LOAEC	Nominal	5	1	8.9	11	2	12.0020429	Zebrafish	larva	Ellis	2012
Sitosterol, beta-	Behavioral	10	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0051073	Beta fish	adult	Clotfelter	2006
Sitosterol, beta-	Behavioral	5000	Unbounded NOAEC	Nominal	2	1	8.9	11	2	12.7681307	Flagfish	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Behavioral	5000	Unbounded NOAEC	Nominal	2	1	8.9	11	2	12.7681307	Japanese medaka	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Behavioral	5000	Unbounded NOAEC	Nominal	2	1	8.9	11	2	12.7681307	Rainbow trout	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Behavioral	1	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0012768	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Circulatory/ Blood Constituents	25	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0319203	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Circulatory/ Blood Constituents	75	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0383044	Rainbow trout	juvenile	Tremblay	1999
Sitosterol, beta-	Developmental	745	Unbounded NOAEC	Measured	1	1	8.9	11	2	3.8049030	Fathead minnow	embryo, larva, juvenile, adult (life-cycle test)	FLINDERS	2014
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	8.9	11	2	5.1072523	Flagfish	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	8.9	11	2	5.1072523	Japanese medaka	embryo to juvenile	Orrego	2011

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Sitosterol, beta-	Developmental	5000	Unbounded LOAEC	Nominal	5	1	8.9	11	2	5.1072523	Rainbow trout	embryo to juvenile	Orrego	2011
Sitosterol, beta-	Growth	745	Unbounded NOAEC	Measured	1	1	8.9	11	2	3.8049030	Fathead minnow	embryo, larva, juvenile, adult (life-cycle test)	FLINDERS	2014
Sitosterol, beta-	Growth	150	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.1915220	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Growth	150	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.1915220	Rainbow trout	juvenile	Tremblay	1999
Sitosterol, beta-	Mortality/ Survival	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Beta fish	adult	Clotfelter	2006
Sitosterol, beta-	Reproductive	745	Unbounded NOAEC	Measured	1	1	8.9	11	2	3.8049030	Fathead minnow	embryo, larva, juvenile, adult (life-cycle test)	FLINDERS	2014
Sitosterol, beta-	Reproductive	75	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0383044	Goldfish	adult	MacLatchy	1997
Sitosterol, beta-	Reproductive	300	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.1532176	Goldfish	adult	MacLatchy	1997
Sitosterol, beta-	Reproductive	10	Bounded NOAEC	Nominal	2	2	8.9	11	2	0.0127681	Rainbow trout	juvenile	Tremblay	1998
Sitosterol, beta-	Reproductive	150	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0766088	Rainbow trout	juvenile	Tremblay	1999

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Sitosterol, beta-	Reproductive	1	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0012768	Siamese fighting fish	adult	Stevenson	2011
Sitosterol, beta-	Reproductive	1	Unbounded NOAEC	Nominal	2	2	8.9	11	2	0.0012768	Siamese fighting fish	adult	Brown	2014
Sitosterol, beta-	Reproductive	1000	Unbounded NOAEC	Nominal	2	2	8.9	11	2	1.2768131	Siamese fighting fish	adult	Brown	2014
Triclosan	Behavioral	10	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0102145	Fathead minnow	larva	Fritsch	2013
Triclosan	Behavioral	0.449	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0011466	Fathead minnow	adult	Schultz	2012
Triclosan	Behavioral	0.45	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0011491	Fathead minnow	larva	Schultz	2012
Triclosan	Behavioral	170	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0868233	Japanese medaka	juvenile	Nassef	2010
Triclosan	Behavioral	34.1	Bounded NOAEC	Measured	1	1	8.9	11	2	0.1741573	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Behavioral	400	Bounded NOAEC	Nominal	2	3	8.9	11	2	0.3404835	Zebrafish	adult	Oliveira	2009
Triclosan	Developmental	0.45	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0011491	Fathead minnow	larva	Schultz	2012
Triclosan	Developmental	10	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0255363	Japanese medaka	larva	Foran	2000

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Triclosan	Developmental	156	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.3983657	Japanese Medaka	embryo	Ishibashi	2004
Triclosan	Developmental	34.1	Bounded NOAEC	Measured	1	1	8.9	11	2	0.1741573	Rainbow trout	embryo, larva	Orvos	2002
Triclosan	Developmental	300	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.7660878	Zebrafish	embryo	Oliveira	2009
Triclosan	Genotoxicity	350	Unbounded NOAEC	Nominal	2	3	8.9	11	2	0.2979231	Zebrafish	adult	Oliveira	2009
Triclosan	Growth	0.449	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0011466	Fathead minnow	adult	Schultz	2012
Triclosan	Growth	136.9	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.3495914	Japanese Medaka	adult	Ishibashi	2004
Triclosan	Growth	101	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.2579162	Mosquitofish	adult	Raut	2010
Triclosan	Histopathology	0.449	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0011466	Fathead minnow	adult	Schultz	2012
Triclosan	Mortality/ Survival	0.449	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0011466	Fathead minnow	adult	Schultz	2012
Triclosan	Mortality/ Survival	200	Bounded NOAEC	Nominal	2	3	8.9	11	2	0.1702417	Zebrafish	adult	Oliveira	2009
Triclosan	Reproductive	0.449	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0011466	Fathead minnow	adult	Schultz	2012

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Triclosan	Reproductive	136.9	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.3495914	Japanese Medaka	adult	Ishibashi	2004
Triclosan	Reproductive	58	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.1481103	Mosquitofish	adult	Raut	2010
Tris(2-butoxyethyl) phosphate	Behavioral	7800	Bounded NOAEC	Nominal	2	3	8.9	11	2	6.6394280	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Tris(2-butoxyethyl) phosphate	Developmental	150	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.3830439	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Developmental	800	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.8171604	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Developmental	4000	Bounded NOAEC	Nominal	2	1	8.9	11	2	10.2145046	Zebrafish	embryo	Han	2014
Tris(2-butoxyethyl) phosphate	Mortality /Survival	2800	Unbounded LOAEC	Nominal	5	3	8.9	11	2	0.9533538	Fathead minnow	Not specified. Mean length of 45mm	Springborn Bionomics, Inc.	1984
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0005107	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Behavioral	0.5	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0005107	Fathead Minnow	larva	Painter	2009
Venlafaxine	Behavioral	50	Unbounded LOAEC	Nominal	5	2	8.9	11	2	0.0255363	Fathead minnow	juvenile	Thomas	2012

Attachment 4-2D. (Continued)

Common Chemical Name	Effect Category	Effect Concentration (ug/L) – INPUT to SV Point Estimate	Type of Effect Concentration	Type of Reported Exposure Concentrations	UFConc (Table 3-14)	UF_{Dura} (Table 3-13)	UF_{Inter} (Table 3-8)	UF_{Intra} (Table 3-12)	UF_{CC} (Table 3-4)	Comprehensive SVL_{OW} Point Estimate (ug/L)	Species Common Name	Life Stage(s) of Exposed Fish	Publication Primary Author, Last Name	Publication Year
Venlafaxine	Developmental	5	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0127681	Fathead Minnow	embryo	Painter	2009
Venlafaxine	Developmental	5	Unbounded NOAEC	Nominal	2	1	8.9	11	2	0.0127681	Fathead Minnow	larva	Painter	2009
Venlafaxine	Developmental	4.35	Unbounded NOAEC	Measured	1	1	8.9	11	2	0.0222165	Zebrafish	embryo	Galus	2013
Venlafaxine	Endocrine/ Hormone	0.2	Unbounded LOAEC	Nominal	5	3	8.9	11	2	0.0000681	Rainbow trout	juvenile	Best	2014
Venlafaxine	Growth	1.104	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0028192	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Histopathology	1.104	Unbounded NOAEC	Measured	1	2	8.9	11	2	0.0028192	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Histopathology	0.5	Unbounded LOAEC	Nominal	5	1	8.9	11	2	0.0005107	Zebrafish	adult	Galus	2013
Venlafaxine	Mortality/ Survival	0.305	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0002596	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	0.305	Unbounded LOAEC	Measured	3	2	8.9	11	2	0.0002596	Fathead Minnow	adult	Schultz	2011
Venlafaxine	Reproductive	0.5	Bounded NOAEC	Nominal	2	1	8.9	11	2	0.0012768	Zebrafish	adult	Galus	2013

Fall 2019


U.S. DEPARTMENT OF THE INTERIOR
MARCH 3, 1849


Great Lakes
RESTORATION