Exhibit 79

1620000 1621000 1622000 1623000 1624000 1625000 1626000 1627000

1772000 1771000 1770000 1769000

Sandia Canyon
Upper Mortandad Canyon
Effluent Canyon
Twomile Canyon

Outfall 022
Outfall 051
Outfall 160
Outfall 181

E-1FW
E-1W
E-1E
E200
TS-1.42 SPRING

TA-03
TA-06
TA-35
TA-40
TA-48
TA-50
TA-55
TA-59
TA-60
TA-61
TA-63
TA-64

STORAX
SIGMA
CRAY
DIAMOND
ENIWETOK
CERRO
FAWN
PIKE
PEDERNAL
GAMMA RAY
NEUTRINO
BETA
ALPHA
JIB
PECOS
ARIES
ARGUS
ATLAS
HELIOS
KHAKI
PAJARITO
TWO MILE MESA
PUYE

Legend

- Spring
- Baseflow Sampling Locations
- Inactive Gage
- NPDES Outfalls
- Paved Roads
- Drainage
- Wetlands
- LANL Tec Areas
- LANL Structures

North American Datum, 1983 (NAD 83)
New Mexico State Plane Coordinate System Central Zone (3002)
Map Number: 21-069-02
Map created by: Ben Sutter, IFPROG Data
Date: June 11, 2021

LA-UR-21-25546

0 250 500 1,000 Feet

N W E S

GIS Program

Los Alamos NATIONAL LABORATORY

2020 TR LANL-01717

1624000 1625000 1626000 1627000 1628000

1771000 1770000 1769000

Upper Mortandad Canyon

TA-60

TA-48

Effluent Canyon

E-1FW

E200

E-1E

E-1W

Outfall 051

Outfall 181

TA-55

TA-64

TA-35

Outfall 160

TA-50

Ten-Site Canyon

TA-63

TA-52

TA-06

Legend

- Baseflow Sampling Locations
- Inactive Gage
- NPDES Outfalls
- Paved Roads
- Drainage
- Wetlands
- LANL Tec Areas
- LANL Structures

North American Datum, 1983 (NAD 83)
New Mexico State Plane Coordinate System Central Zone (3002)
Map Number: 21-069-01
Map created by: Ben Sutter, IFPROG Data
Date: June 9, 2021

LA-UR-21-25546

0 125 250 500 Feet

N W E S

GIS Program

Los Alamos NATIONAL LABORATORY

2020 TR LANL-01718

Exhibit 80

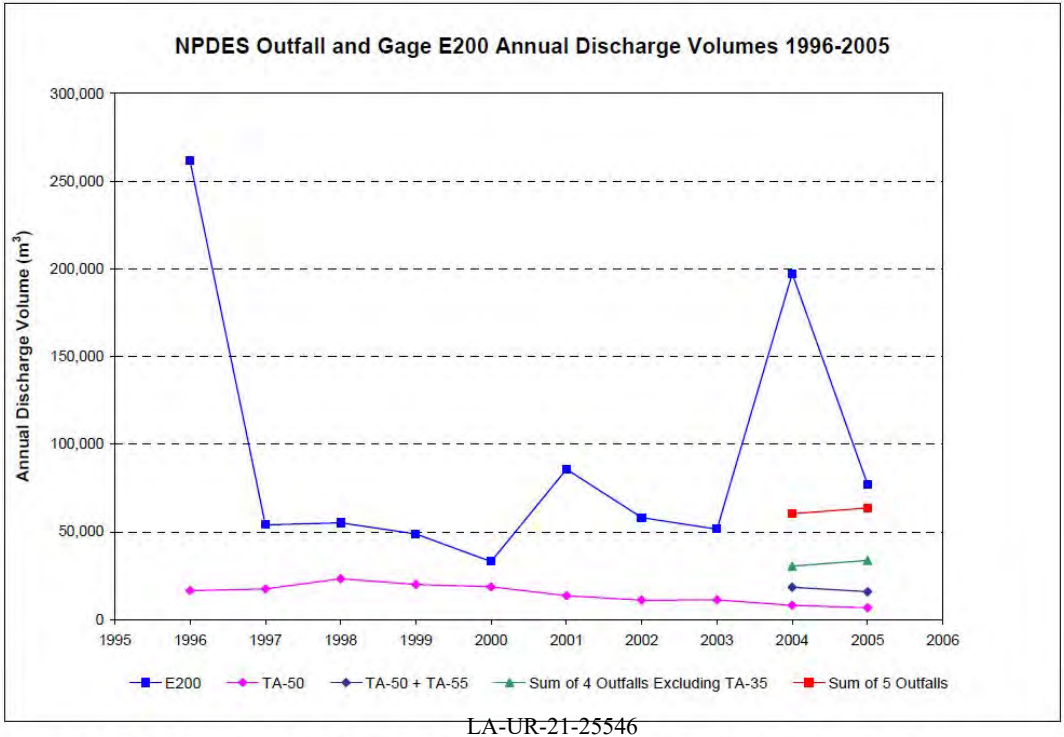
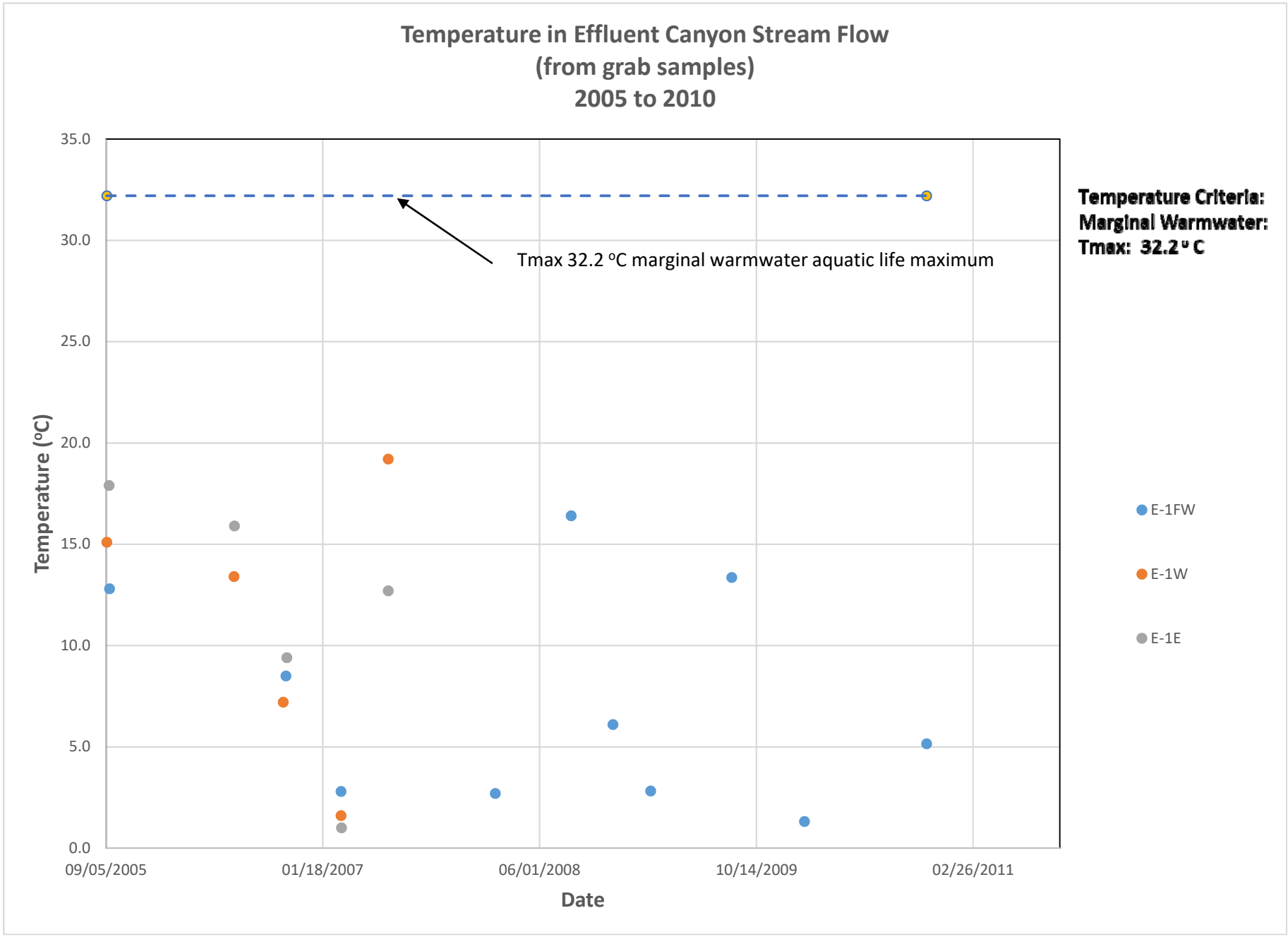
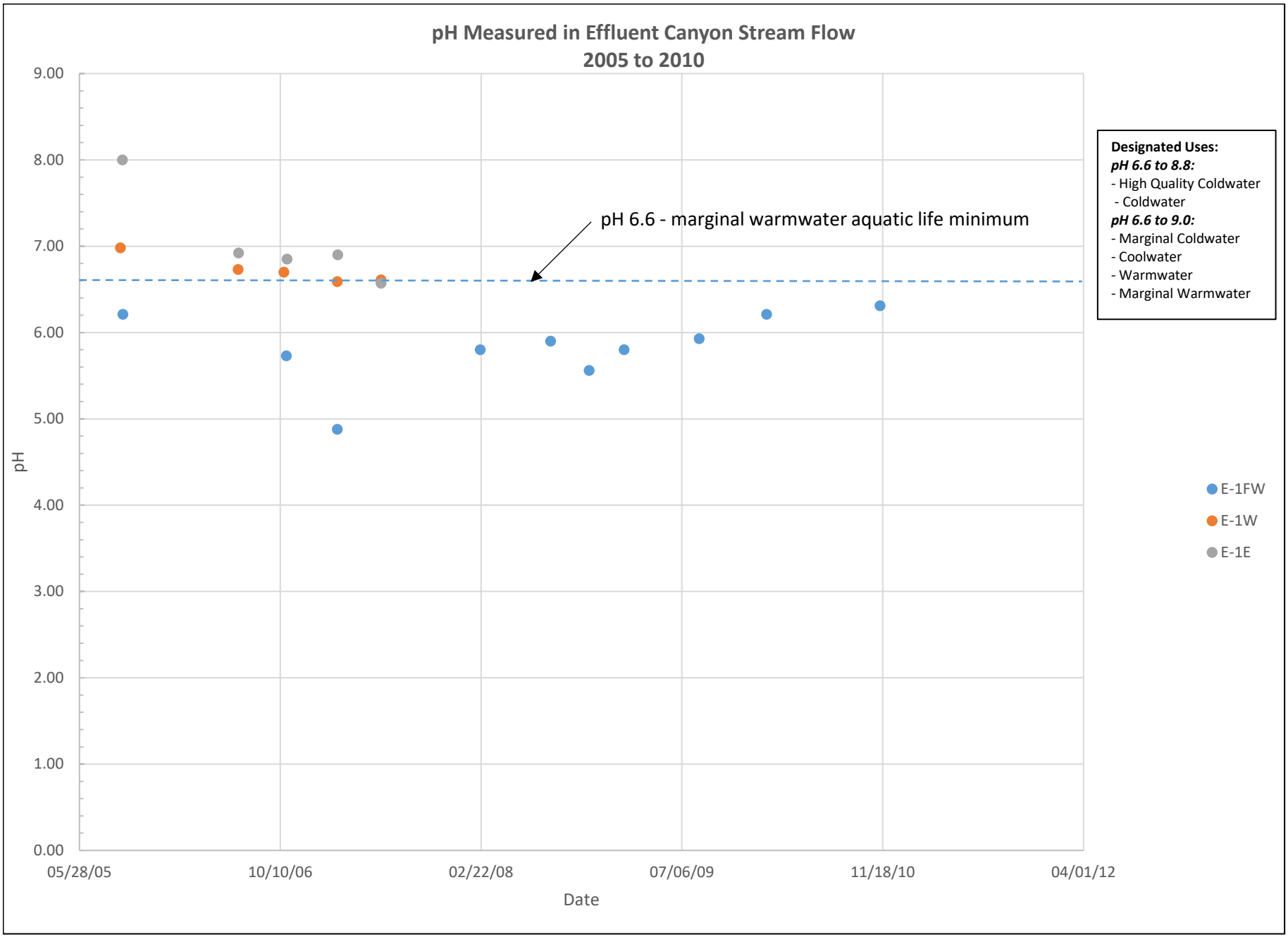


Figure 7.2-2. Comparison of NPDES outfall and gage E200 discharge volumes

Exhibit 81


Temperature in Effluent Canyon Stream Flow
(from grab samples)
2005 to 2010
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Temperature (°C)
09/05/2005
01/18/2007
06/01/2008
10/14/2009
02/26/2011
Date
Tmax 32.2 °C marginal warmwater aquatic life maximum
Temperature Criteria:
Marginal Warmwater:
Tmax: 32.2 ° C
E-1FW
E-1W
E-1E


pH Measured in Effluent Canyon Stream Flow
2005 to 2010
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
pH
pH 6.6 - marginal warmwater aquatic life minimum
05/28/05
10/10/06
02/22/08
07/06/09
11/18/10
04/01/12
Date
Designated Uses:
pH 6.6 to 8.8:
- High Quality Coldwater
- Coldwater
pH 6.6 to 9.0:
- Marginal Coldwater
- Coolwater
- Warmwater
- Marginal Warmwater
E-1FW
E-1W
E-1E

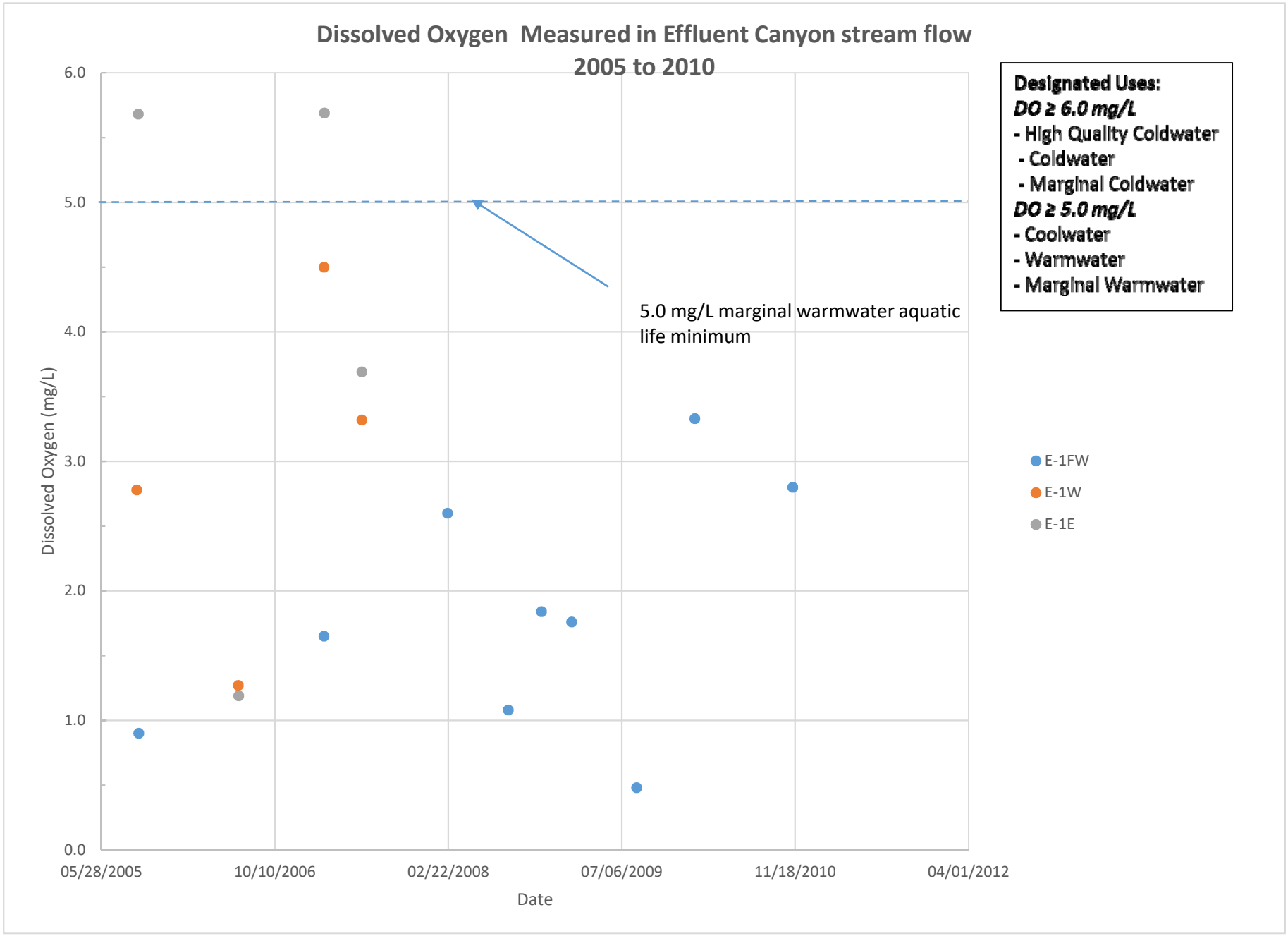
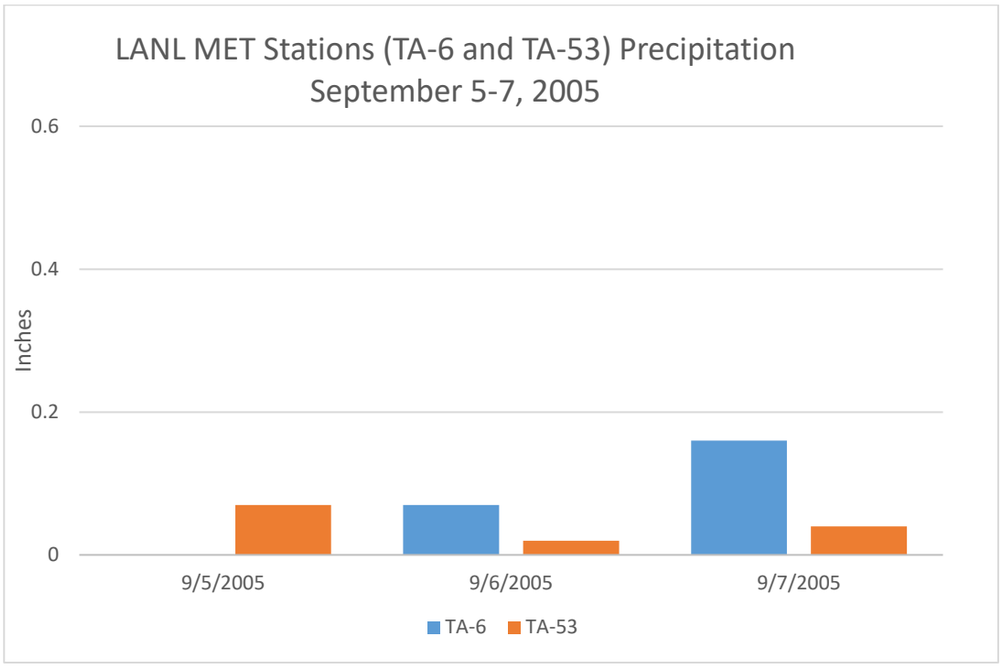
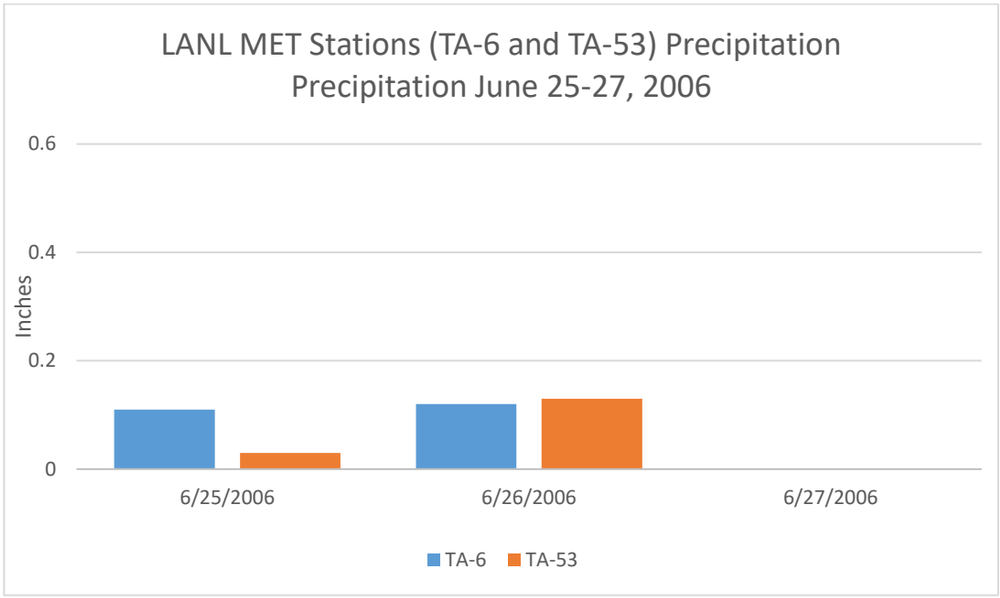
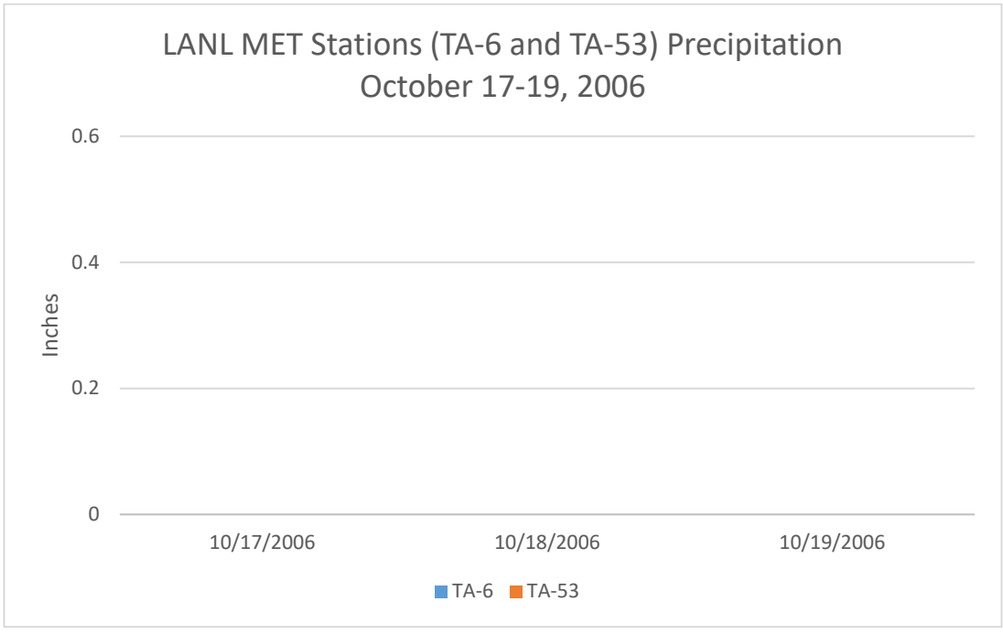
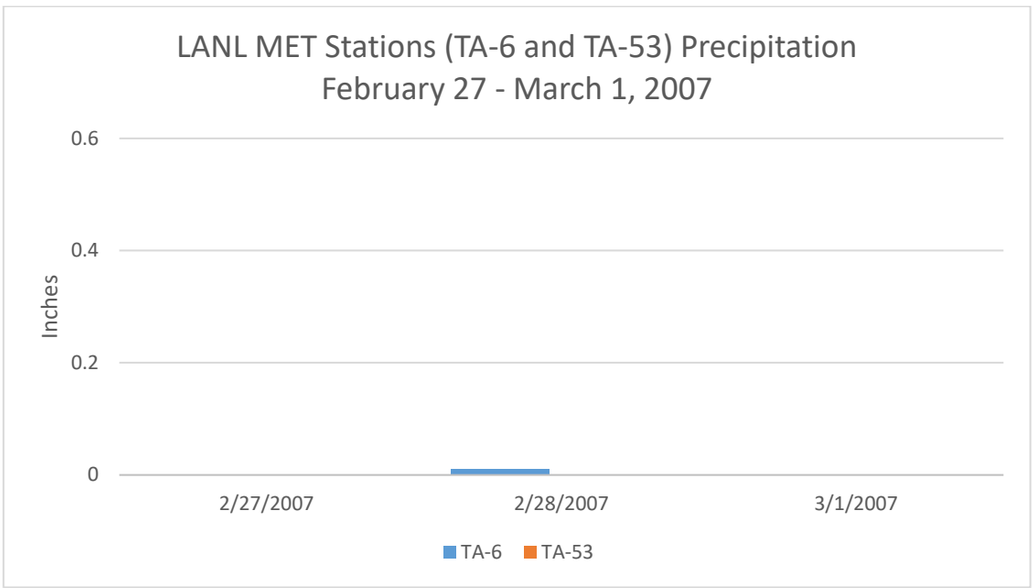

Dissolved Oxygen Measured in Effluent Canyon stream flow
2005 to 2010
Designated Uses:
DO ≥ 6.0 mg/L
- High Quality Coldwater
- Coldwater
- Marginal Coldwater
DO ≥ 5.0 mg/L
- Coolwater
- Warmwater
- Marginal Warmwater
5.0 mg/L marginal warmwater aquatic life minimum
E-1FW
E-1W
E-1E
Dissolved Oxygen (mg/L)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
05/28/2005
10/10/2006
02/22/2008
07/06/2009
11/18/2010
04/01/2012
Date

Exhibit 82


LANL MET Stations (TA-6 and TA-53) Precipitation
September 5-7, 2005
0.6
0.4
0.2
0
Inches
9/5/2005
9/6/2005
9/7/2005
TA-6
TA-53


LANL MET Stations (TA-6 and TA-53) Precipitation
Precipitation June 25-27, 2006
0.6
0.4
0.2
0
Inches
6/25/2006
6/26/2006
6/27/2006
TA-6
TA-53


LANL MET Stations (TA-6 and TA-53) Precipitation
October 17-19, 2006
0.6
0.4
0.2
0
Inches
10/17/2006
10/18/2006
10/19/2006
TA-6
TA-53


LANL MET Stations (TA-6 and TA-53) Precipitation
February 27 - March 1, 2007
0.6
0.4
0.2
0
Inches
2/27/2007
2/28/2007
3/1/2007
TA-6
TA-53

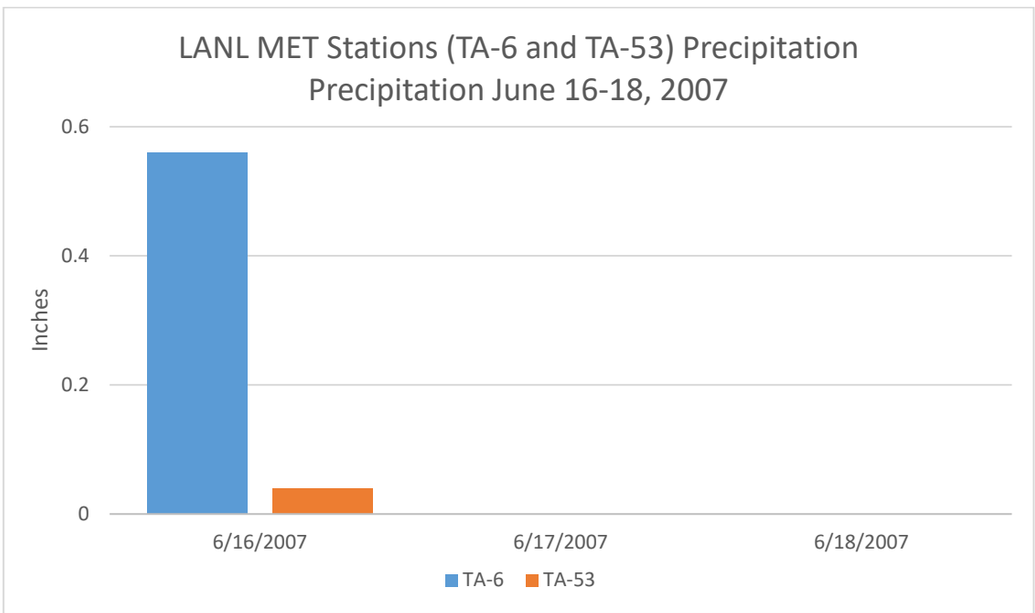

LANL MET Stations (TA-6 and TA-53) Precipitation
Precipitation June 16-18, 2007
0.6
0.4
0.2
0
Inches
6/16/2007
6/17/2007
6/18/2007
TA-6
TA-53

Exhibit 83

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 5 1997

OFFICE OF WATER

MEMORANDUM

SUBJECT: Establishing Site Specific Aquatic Life Criteria Equal to Natural Background

FROM: Tudor T. Davies, Director
Office of Science and Technology

TO: Water Management Division Directors, Regions 1-10
State and Tribal Water Quality Management Program Directors

In the course of reviewing State and Tribal water quality standards (WQS), EPA has identified several issues pertaining to the establishment of site specific numeric criteria on the basis of natural background conditions. EPA is issuing this policy to provide greater clarity and direction for States and Tribes who are considering establishing site specific criteria equal to natural background conditions, and for EPA Regional Offices reviewing State and Tribal water quality management programs.

Background

Site specific criteria are allowed by regulation and are subject to EPA review and approval. The Federal water quality standards regulation at 40 CFR 131.11(b)(1) requires States and authorized Tribes to adopt numeric water quality criteria that are based on section 304(a) criteria, section 304(a) criteria modified to reflect site-specific conditions, or other scientifically defensible methods. Under 40 CFR 131.5(a)(2), EPA reviews State WQS to determine whether a State has adopted criteria to protect the designated uses. Existing guidance and practice are that EPA will approve site specific criteria developed on the basis of sound scientific rationales.

Currently, EPA guidance has specified three procedures for States and Tribes to follow in deriving site specific criteria. These are the Recalculation Procedure, the Water-Effect Ratio Procedure and the Resident Species Procedure. These procedures can be found in the *Water Quality Standards Handbook* (EPA-823-B940005a, 1994). EPA also recognizes there may be naturally occurring concentrations of pollutants which may exceed the national criteria published under section 304(a) of the Clean Water Act.

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Policy

This policy applies only to site specific numeric aquatic life criteria based on natural background. States and Tribes may establish site specific numeric aquatic life water quality criteria by setting the criteria value equal to *natural* background. Natural background is defined as background concentration due *only* to non-anthropogenic sources, i.e., non-manmade sources. In setting criteria equal to natural background the State or Tribe should, at a minimum, include in their water quality standards:

(1) a definition of natural background consistent with the above;
(2) a provision that site specific criteria may be set equal to natural background;
(3) a procedure for determining natural background, or alternatively, a reference in their water quality standards to another document describing the binding procedure that will be used.

Discussion

A State or Tribal procedure for determining natural background will need to be specific enough to establish natural background concentration accurately and reproducibly. States and Tribes should also provide for public notice and comment on the definition, the provision, the procedure and the site specific numeric criteria derived from the procedure. The State or Tribe will need to document the resulting site specific numeric criteria in the State or Tribal water quality standards, including specifying the water body segment to which the site specific criteria apply. This can be accomplished through adopting the site specific criteria into the State or Tribal WQS, or, alternatively, by appending the site specific criteria to the WQS. In either case, the State or Tribe must comply with the public participation requirements of 40 CFR 131.20 and 40 CFR Part 25, and State and Tribal citizens should be able to readily determine the water quality criteria applicable to specific water bodies.

For aquatic life uses, where the natural background concentration for a specific parameter is documented, by definition that concentration is sufficient to support the level of aquatic life expected to occur naturally at the site absent any interference by humans. The State or Tribe should consider refining the designated use for the water body to more precisely define the existing aquatic life use.

This policy does not apply to human health uses. For human health uses, where the natural background concentration is documented, this new information should result in, at a minimum, a re-evaluation of the human health use designation. Where the new background information documents that the natural background concentration does not support a human health use previously believed attained, it may be prudent for the State or Tribe to change the human health use to one the natural background concentration will support (e.g., from drinking water supply to drinking water supply only after treatment).

Conclusion

This policy explains and clarifies the use of natural background conditions in establishing site specific criteria for protection of aquatic life uses. In addition to the three procedures listed above for deriving site specific criteria as discussed above, States and Tribes can address natural background conditions through refining the designated use to more accurately reflect the aquatic community present within the stream segment. EPA recognizes that there are other options available to States/Tribes to account for other ambient conditions (e.g., concentrations due to non-natural, man-made conditions) which exceed the national criteria. One such option is for a State or Tribe to conduct a Use Attainability Analysis, consistent with the requirements of 40 CFR 131.10, and adopt a use which is less than the 101(a) goal uses of the Clean Water Act, e.g., less than "fishable/swimmable", or modify a 101(a) goal use such that less stringent criteria are required. In any case, the existing uses of the water body segment must be maintained and protected.

If you have any questions or concerns regarding this policy, please contact me or have your staff contact Elizabeth Southerland, Acting Director, Standards and Applied Science Division, at 202-260-3966.

cc: Lepow, OGC
Wayland, OWOW
Cook, OWM
Dougherty, OGWDW

2020 TR LANL-01731

Exhibit 84

WHITE PAPER

AQUATIC LIFE CRITERIA FOR CONTAMINANTS OF EMERGING CONCERN

PART I

GENERAL CHALLENGES AND RECOMMENDATIONS

Prepared by the
OW/ORD Emerging Contaminants Workgroup

June 03, 2008

NOTICE

THIS DOCUMENT IS AN INTERNAL PLANNING DOCUMENT

It has been prepared for the purpose of Research & Development Planning. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency guidance or policy.

DRAFT DOCUMENT

2020 TR LANL-01733

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List of Acronyms:

ACR	Acute to Chronic Ratio
ALC	Aquatic Life Criteria
Ah	Aryl Hydrocarbon (receptor)
AV	Acute (toxicity) value
AWQC	Ambient Water Quality Criteria
CCC	Criterion Continuous Concentration
CEC	Contaminants of Emerging Concern
CMC	Criterion Maximum Concentration
CV	Chronic (toxicity) value
CWA	Clean Water Act
CYP	Cytochrome enzymes (P450)
EDC	Endocrine Disrupting Chemicals
E2	Estradiol (natural estrogen)
EE2	Ethynylestradiol (synthetic pharmaceutical estrogen)
ELS	Early Life-Stage (toxicity test)
EPA	Environmental Protection Agency
FAV	Final Acute Value
FACR	Final Acute to Chronic Ratio
GMAV	Genus Mean Acute Value
GMCV	Genus Mean Chronic Value
HPG	Hypothalamic-Pituitary-Gonadal (axis)
HPT	Hypothalamic-Pituitary-Thyroid (axis)
LOEC	Lowest Observed Effect Concentration
MDR	Minimum Data Requirement
MOA	Mode of Action
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Development and Cooperation
OWC	Organic Wastewater Contaminant
PBDE	Polybrominated Diphenyl Ether
PPCP	Pharmaceutical and Personal Care Product
POP	Persistent Organic Pollutant
SMAV	Species Mean Acute Value
TBT	Tributyltin
USGS	United States Geological Survey
VTG	Vitellogenin protein
vtg	Vitellogenin gene transcript
WWTP	Wastewater Treatment Plant

1.0 INTRODUCTION

Under the United States Clean Water Act (CWA) (33 U.S.C. Sections 1251-1387), EPA is required to take a number of actions to protect and restore the ecological integrity of the Nation's water bodies. Under Section 304(a) of the CWA, EPA must develop and publish ambient water quality criteria. Ambient water quality criteria (AWQC) are levels of individual pollutants, water quality characteristics, or descriptions of conditions of a water body that, if met, should protect the designated use(s) of the water. Examples of designated uses of a water body include swimming, drinking water, fishing, fish spawning, and navigation. States and authorized tribes establish designated uses for their water bodies. AWQC are recommended guidance that states and tribes may use as part of their water quality standards to protect water bodies for their designated use from chemical pollutants.

AWQC for aquatic life (aquatic life criteria, ALC) developed under Section 304(a) reflect the "latest scientific knowledge" concerning "all identifiable effects" of the pollutant in question. These criteria are based solely on data and scientific determinations on the relationship between environmental concentrations of the pollutant and its effects. Criteria do not consider social and economic impacts, or the technological feasibility of meeting the chemical concentration values in ambient water. Since the early 1980's, EPA has been developing ALC to protect aquatic organisms from chemical specific pollutants under Section 304(a) of the CWA. In 1985, EPA published *Guidelines for Deriving Numerical National Water Quality Criteria for the Protection of Aquatic Organisms and Their Uses* (hereafter referred to as the "*Guidelines*"; Stephan et al. 1985). The *Guidelines* has provided uniformity and transparency in the derivation methodology of ALC for a large number of compounds among several classes of chemicals. The majority of EPA's currently recommended ALC have been derived using the methods outlined in the *Guidelines*.

While the *Guidelines* remain the primary instrument the Agency uses to meet its broad objectives for the development of ALC, there have been many advances in aquatic sciences, aquatic and wildlife toxicology, population modeling, and ecological risk assessment that are relevant to deriving ALC. Some of the advances have been addressed through supplemental guidance on the derivation or site-specific modification of criteria (Prothro 1993; U.S. EPA 1994a), while others have been incorporated directly into derivation of individual ALC for certain chemicals (e.g., saltwater chronic aquatic life criterion for tributyltin, U.S. EPA 2003). Recently, considerable attention has been generated by a widely ranging group of chemicals termed, in this document, contaminants of emerging concern (CECs). As is discussed in the body of this document, some of these CECs present challenges for the application of the *Guidelines* to ALC development.

1.1 What is a Contaminant of Emerging Concern?

The term "contaminant of emerging concern" is being used within the Office of Water to replace "emerging contaminant," a term that has been used loosely since the mid-1990s by EPA and others to identify chemicals and other substances that have no regulatory standard, have been recently "discovered" in natural streams (often because of improved analytical chemistry detection levels), and potentially cause deleterious effects in aquatic life at environmentally

relevant concentrations. They are pollutants not currently included in routine monitoring programs and may be candidates for future regulation depending on their (eco)toxicity, potential health effects, public perception, and frequency of occurrence in environmental media. CECs are not necessarily new chemicals. They include pollutants that have often been present in the environment, but whose presence and significance are only now being evaluated.

CECs include several types of chemicals:

- Persistent organic pollutants (POPs) such as polybrominated diphenyl ethers (PBDEs; used in flame retardants, furniture foam, plastics, etc.) and other global organic contaminants such as perfluorinated organic acids;
- Pharmaceuticals and personal care products (PPCPs), including a wide suite of human prescribed drugs (e.g., antidepressants, blood pressure), over-the-counter medications (e.g., ibuprofen), bactericides (e.g., triclosan), sunscreens, synthetic musks;
- Veterinary medicines such as antimicrobials, antibiotics, anti-fungals, growth promoters and hormones;
- Endocrine-disrupting chemicals (EDCs), including synthetic estrogens (e.g.,17α-ethynylestradiol, which also is a PCPP) and androgens (e.g., trenbolone, a veterinary drug), naturally occurring estrogens (e.g.,17ß-estradiol, testosterone), as well as many others (e.g., organochlorine pesticides, alkylphenols) capable of modulating normal hormonal functions and steroidal synthesis in aquatic organisms;
- Nanomaterials such as carbon nanotubes or nano-scale particulate titanium dioxide, of which little is known about either their environmental fate or effects.

1.2 Why is EPA Concerned with CECs?

The variety of chemicals labeled as CECs leads to a variety of concerns for EPA. Widespread uses, some indication of chemical persistence, effects found in natural systems, and public concerns have made clear the need for EPA to develop criteria that can be used to help assess and manage potential risk of some CECs in the aquatic environment. A recent U.S. Geological Survey (USGS) reconnaissance study (Kolpin et al. 2002) provides a good example of the prevalence of a wide range of CECs in U.S. streams. Improved analytical chemistry techniques were used to document the occurrence of what the authors called organic wastewater contaminants (OWCs) being released into surface waters from wastewater treatment plants (WWTPs). The targeted OWCs included PPCPs, veterinary medicines and other EDCs. The investigators found at least one of 95 different target OWCs in 80 percent of the 139 streams sampled. A median of seven, and as many as 38, OWCs were found in single samples.

The use and occurrence patterns associated with CECs are varied. Some CECs are similar to conventional toxic pollutants in that they are associated with industrial releases, whereas many others are used by the general public every day in homes, on farms, by businesses and industry (Daughton and Ternes 1999). PPCPs acting as EDCs can be released directly to the environment after passing through wastewater treatment processes, which are typically not designed to remove these pollutants from the effluent (Halling-Sorensen et al. 1998). Sludge from secondary treatment processes are land-applied as biosolids, supplying CECs which may leach or run off into nearby bodies of water. Pharmaceuticals used in animal feeding operations may be released

to the environment in animal wastes via direct discharge of aquaculture products (i.e., antibiotics), the excretion of substances in animal urine and feces of livestock animals, and the washoff of topical treatments from livestock animals (Boxall et al. 2003).

EDCs discharged at WWTPs are one group of CECs with potentially widespread environmental effects (Folmar et al. 1996; Folmar et al. 2001; Jobling et al. 1998; Woodling et al. 2006). Although particular concern has been expressed about the anthropogenic EDCs, there are also natural estrogens (estradiol and its metabolites estriol and estrone) entering the aquatic environment through wastewater discharge and excretion from domestic animals. Furthermore, little is known about the environmental occurrence, fate and, transport for any of these compounds after they enter aquatic ecosystems. Many of the man-made compounds have been in use for a long time, and there is concern about pharmacologically active ingredients and personal care products that are designed to stimulate a physiological response in humans, plants, and animals (Daughton and Ternes 1999).

Frequent detection of compounds by itself does not constitute a need for ALC. Rather, criteria development for CECs needs to focus efforts on chemicals that demonstrate a reasonable potential to adversely affect aquatic life. Of CECs now known to be found in some surface waters of the U.S., EDCs have received the most attention because field studies from around the world have demonstrated that very low concentrations of some of these compounds can significantly impact natural populations of aquatic vertebrates. For example, observational field studies (Jobling et al. 1998) have shown a high occurrence of intersex (the presence of both male and female characteristics) in wild populations of a fish known as roach (*Rutilus rutilus*) in rivers in the United Kingdom that are downstream from WWTPs. Similar results have recently been reported for white sucker (*Catastomus commersoni*) in northern Colorado, U.S.A (Woodling et al. 2006). In a multiyear study by Kidd et al. (2007), the authors showed that environmentally relevant concentrations of ethynylestradiol, EE2, caused reproductive failure and near collapse of a natural fathead minnow population in an experimental lake, and also had deleterious effects on the reproductive biology of the pearl dace. These direct effects resulting in loss of forage fish have led to cascading effects on the lake trout population due to lack of prey (Kidd, personal communication). Researchers from the U.S. Geological Survey (USGS) have observed intersex and testis-ova (the presence of eggs in the testis) in bass species collected from the Potomac River and its tributaries in West Virginia, Maryland, and Washington DC, and also quantified EDCs in their blood (Blazer et al. 2007; Chambers and Leiker 2006). The occurrence of intersex fish in the Potomac River, as well as documented occurrence of this and related effects in other waters of the US and internationally, prompted Congressional hearings that were held in October 2006 to inquire about the "State of the Science on EDCs in the Environment," as well as EPA activities associated with EDCs.

1.3 Purpose and Organization of This White Paper

The purpose of this white paper is to provide general guidance on how criteria development for CECs could be facilitated through a supplemental interpretation of the *Guidelines*, with particular attention to PPCPs with an EDC mode of action (MOA). Section 2 of this part (Part I) of the white paper describes the *Guidelines* procedures and identifies several areas in which these

procedures could be modified to address potential limitations for deriving criteria for CECs. Section 3 expands upon the areas of concern with respect to specific toxicological characteristics of some CECs. Section 4 summarizes these concerns and provides recommendations that could aid in the development of criteria for CECs in a resource efficient manner that takes best advantage of existing knowledge. Part II of this white paper further describes these concerns and recommendations using data for the synthetic pharmaceutical estrogen EE2.

2.0 CURRENT ALC METHODOLOGY

The *Guidelines* specify various data and procedural recommendations for criteria derivation, and also define general risk management goals for criteria, which are to provide a high level of protection for aquatic communities and for important species in these communities. ALC are defined to consist of two concentrations – the Criterion Maximum Concentration (CMC), intended to protect against severe acute effects, and the Criterion Continuous Concentration (CCC), intended to protect against longer term effects on survival, growth, and reproduction. The CMC is used in criteria to limit peak exposures by requiring that 1-hour averages of exposure concentrations not exceed the CMC more often than once in three years on average. The CCC is used in criteria to limit more prolonged exposures by requiring that 4-day averages of exposure concentrations not exceed the CCC more often than once in three years on average.

The CMC and CCC are usually derived from laboratory toxicity test results using specific standard procedures described in the *Guidelines*, but the *Guidelines* also have general provisions for deviating from these procedures as warranted by available information. The following text will first give an overview of the data requirements and calculations in the standard procedures, and then discuss how these procedures might vary under the umbrella of the *Guidelines*.

2.1 Standard ALC Derivation Procedures

The CMC is determined based on available Acute Values (AVs) – median lethal concentrations (LC_{50}s) or median effect (for a severe acute effect such as immobilization) concentrations (EC_{50}s) from aquatic animal acute toxicity tests (48- to 96-hours long) meeting certain data quality requirements. To compute a CMC, the *Guidelines* require that acceptable AVs be available for at least eight genera with a specified taxonomic diversity, in order to address a wide variety of the organisms constituting an aquatic animal community. These minimum data requirements include three vertebrates (a salmonid fish, a fish from a family other than salmonidae, and a species from a third chordate family) and five invertebrates (a planktonic crustacean, a benthic crustacean, an insect, a species from a phylum other than Chordata or Arthropoda, and a species from another order of insect or a fourth phylum).

For each genus, a Genus Mean Acute Value (GMAV) is calculated by first taking the geometric mean of the available AVs within each species (Species Mean Acute Value, SMAV) and then the geometric mean of the SMAVs within the genus. The fifth percentile of the set of GMAVs so obtained is calculated based on a specified estimation method, and designated the Final Acute Value (FAV). The FAV is then lowered to the SMAV for an important, sensitive species if appropriate. The CMC is set equal to half of the FAV to represent a low level of effect for the fifth percentile genus, rather than 50% effect.

The CCC is generally determined based on available Chronic Values (CVs), which are either (a) the geometric mean of the highest no-observed-effect concentration (NOEC) and lowest

observed effect concentration (LOEC) for effects on survival, growth, or reproduction in aquatic animal chronic tests or (b) in some recent criteria (e.g., ammonia), the EC_{20} in such tests based on concentration-effect regression analyses. Chronic tests for invertebrate species are required to include the entire life-cycle, but for fish partial life-cycle and early life-stage (ELS) testing protocols are accepted, the latter not including reproductive endpoints and not used if life-cycle or partial life-cycle tests are available and show more sensitive adverse effects.

If CVs are available for at least eight genera with the required taxonomic diversity, the CCC is set to the fifth percentile of Genus Mean Chronic Values (GMCVs), by the same procedure used to derive an FAV from GMAVs. Otherwise, the CCC is set to the FAV divided by a Final Acute Chronic Ratio" (FACR) that is based on acute to chronic ratios (ACRs – the ratio of the AV to the CV from parallel acute and chronic tests) for at least three species with a specified taxonomic diversity. The CCC can also be based on plant toxicity data if aquatic plants are more sensitive than aquatic animals, or on other data as deemed scientifically justified.

Further details on test requirements and calculation methods for the CMC and CCC are specified in the *Guidelines*, including deriving criteria that are a function of water quality characteristics.

2.2 Alternatives for ALC Derivation

The procedures described above enable broad application to toxic chemicals generally, and are only constrained by specific data requirements for quality and minimum taxonomic representation. Since they are not restricted with respect to specific types of chemicals, there is no reason to suppose that the standard data requirements and procedures specified by the *Guidelines* are any more or less applicable to CECs than to the chemicals for which criteria have already been developed. The *Guidelines* anticipated that rote application of the basic procedures may not yield the most appropriate criteria; consequently, the *Guidelines* provide flexibility when appropriate for deviation from the normal procedures regardless of the type of chemical, as indicated by the following provisions (hereafter referred to as the "Good Science" clauses:

> *"These National Guidelines should be modified whenever sound scientific evidence indicates that a national criterion produced using these Guidelines would probably be substantially overprotective or underprotective of aquatic organisms and their uses on a national basis."* (p. 18).
>
> *"On the basis of all available pertinent laboratory and field information, determine if the criterion is consistent with sound scientific evidence. If it is not, another criterion, either higher or lower, should be derived using appropriate modifications of these Guidelines."* (p. 57).

In addition, although the standard procedures in the *Guidelines* for deriving a CMC and CCC use only toxicity tests meeting certain requirements, the *Guidelines* also mandate the collation and examination of other data that might show effects that should be considered in criteria derivation:

> *"Pertinent information that could not be used in earlier sections might be available concerning adverse effects on aquatic organisms and their uses. The most important of these are data on ... any other adverse effect that has been shown to be biologically important. Especially important are data for species for which no other data are available. ... Such data might affect a criterion if the data were obtained with an important species, the test concentrations were measured, and the endpoint was biologically important."* (p. 54).

While alternatives are allowed when a specific situation dictates, the *Guidelines* still require that any changes in the procedures are consistent with the level of protection represented by the standard procedures:

> *"Derivation of numerical national water quality criteria for aquatic organisms and their uses is a complex process and requires knowledge in many areas of aquatic toxicology; any deviation from these Guidelines should be carefully considered to ensure that it is consistent with other parts of these Guidelines."* (p. iv).

Therefore, for the development of criteria for any chemical, the general strategy should be to start with the standard *Guidelines* procedures and then to adapt those procedures as warranted by available information on the effects of the chemical. This strategy applies to CECs as well, although certain considerations might more consistently be important for CECs. Specific attributes of CECs that might affect criteria derivations are considered in Section 3 of this paper, but several issues are introduced here that are of general concern.

Are data on acute toxicity needed for risk assessments?

Some chemicals are not acutely toxic even at concentrations so high that they could not possibly occur in the environment (e.g., at the chemical solubility, or exceeding exposures possible based on known chemical production and discharges). The acute lethality of some classes of chemicals might be measurable, but would occur at environmental concentrations so much higher than those affecting reproduction, growth, or chronic survival that, in practice, environmental exposures will always be far below acutely lethal levels if those exposures are managed to limit chronic effects. Therefore, derivation of the CMC might be unnecessary or impossible. Thus, if the existing data indicate that it is reasonably certain that acute toxicity would not occur at environmentally relevant concentrations, conducting additional acute tests is likely to be unwarranted.

Even if a CMC is not needed, another use of acute toxicity data is for developing "acute to chronic ratios" (ACRs) that are used with the FAV to calculate the CCC (see pages 40-42 in the *Guidelines*) , so that dropping acute testing requirements must consider this consequence as well. However, if acute effect concentrations are extremely high compared to chronic effect concentrations (large ACRs), whether the ACR approach should be even used warrants some consideration. Large ACRs are not, *per se*, less accurate than low ACRs, provided acute and chronic effect concentrations are well defined and the issue is simply extrapolating from acute to chronic toxicity within a species. However, for criteria calculations, the FACR needs to be a ratio that extrapolates from the fifth percentile of the acute effect concentration distribution to the fifth percentile of the chronic effect distribution. This requires appropriately combining ACR

information across species, the accuracy of which might be affected by large ACRs even if the accuracy of the individual ACRs is not. Therefore, in addition to not needing a CMC, extreme acute tolerance might also warrant direct calculation of the CCC rather than using the ACR approach, and thus eliminate the need for fulfilling all of the minimum acute toxicity test requirements as specified by the *Guidelines*.

How should data requirements for tolerant taxa be addressed?
The fifth percentile calculation methods for the CMC (as well as the CCC if the eight minimum data requirements noted above are met) require actual GMAV (or GMCV) values only for the four most sensitive genera. For more tolerant genera, it is only necessary to know that these toxicity values are greater than those of the four sensitive species. Therefore, toxicity test results that report "greater than" effect concentrations are acceptable for the tolerant taxa, and in fact are used in various criteria already.

If chronic tests have not already been done on some taxa needed for the minimum data requirements, but which are known to be tolerant, testing resources might be wasted by generating numbers that will not affect results. If methods such as inter-chemical or inter-species extrapolation methods, or assays (e.g., *in vitro* tests, biomarkers) that have been related to apical effects such as reductions in growth, survival, or reproduction can demonstrate these taxa to be insensitive compared to other taxa, actual chronic tests on these taxa may not be needed. In other words, can minimum data requirements for tolerant taxa be satisfied by some type of estimation rather than by an actual test result?

However, adding estimated data can become a rather open-ended process. Therefore, consideration must be given to how many estimated values should be allowed, relative to measured values, to produce an appropriate distribution of taxa in the data set used for criteria derivation.

Should fish chronic tests be required to address reproduction?
For chemicals (e.g., environmental estrogens) for which reproductive toxicity is of most concern, the allowance in the *Guidelines* for using ELS tests might need reconsideration. The *Guidelines* already give priority to life-cycle and partial life-cycle tests when they are available and show greater sensitivity than ELS tests. However, other information (from other species, similar chemicals, knowledge of the MOA) regarding latent or multigenerational reproductive effects may demonstrate the importance of sexual development and reproduction, so as to establish a basis for not considering ELS test results (or even partial life-cycle tests), but rather requiring life-cycle tests for fish.

What endpoints can serve as surrogates for traditional chronic endpoints?
Although chronic criteria are and will continue to be based on effects on reproduction, growth, and survival, another issue is whether only toxicity data directly addressing these endpoints is acceptable. Is there additional information (e.g., sub-organismal biomarkers, behavioral data) that can be used in criteria derivation because they are adequately correlated to reproduction, growth, and survival? Use of such data would be consistent with the *Guidelines* requirements to examine all pertinent data and make modifications to the criteria derivation procedures that are consistent with sound scientific evidence

2.3 Precedent for Deviating from Basic ALC Derivation Procedures

The recent ALC document for tributyltin (TBT) provides a good example of some of the types of procedural criteria modifications discussed above. TBT is a highly toxic biocide that has been used extensively in anti-fouling paint to protect the hulls of large ocean-going ships. It is deemed a problem in the aquatic environment because it is extremely toxic to non-target organisms, and has been linked to imposex (the superimposition of male anatomical characteristics on females) and to immuno-supression in snails and bivalves (U.S. EPA 2003). The concentrations reported to cause imposex in the laboratory are lower (range: 0.0093 to 0.0334 µg/L) than the FCV (0.0658 µg/L) calculated using the standard ALC derivation procedures (U.S. EPA 2003). The low effect concentrations established for female gastropods in the laboratory were subsequently corroborated in field studies. The CCC was lowered (to 0.0074 µg/L) based on the judgment that these effects were relevant for the risks of TBT to gastropod reproduction.

3.0 CHARACTERISTICS OF CECS AND THEIR INFLUENCE ON ALC DEVELOPMENT

As described in Section 1.0, chemicals become labeled as CECs for a variety of reasons, many of which have relatively little to do with their toxicological characteristics. Consequently, the Guidelines cannot be interpreted or modified in one particular way that would be universally appropriate for all CECs. However, some characteristics may be shared by various CECs, such that discussing the implications of these characteristics in the context of deriving water quality criteria is worthwhile. The expected outcome is additional guidance addressing key issues that may arise and how best to accommodate these issues in deriving criteria.

Much of the technical discussion that follows is centered on EDCs and, even more specifically, around chemicals that interact with the hypothalamic/pituitary/gonadal (HPG) axis. Endocrine function controlled via the HPG axis involves hormones broadly known as estrogens ("female" hormones such as estradiol) and androgens ("male" hormones such as testosterone), along with the body tissues and biochemical machinery with which they interact. Effects on this part of the endocrine system of various aquatic species have been documented in the literature, and publicized in the media, making toxicological disruption of this mechanism a good choice for discussing CECs in the context of the *Guidelines.* However, these types of substances are only a subset of EDCs, and an even smaller subset of CECs as a whole. While much of the discussion that follows uses HPG-active chemicals as a point of reference, the concepts presented may be useful in the derivation of ALC for many other chemicals as well. It is the principles more than the specifics that are important in considering the content of this report.

3.1 Characteristics of HPG-Active EDCs

While estrogenic and androgenic hormones are a core component of the HPG axis, this system also includes a much larger group of tissues and biochemical machinery within the body which, in vertebrates, govern sexual development, maturation, and reproduction. Commensurate with this complexity, there are many places within the system that environmental chemicals may act to modify the normal function of the HPG-axis. Thinking simply of "estrogenicity" or "androgenicity" as toxicological modes of action is still too broad – these categorical classes are more the outward "symptoms" of disruption in the HPG axis than they are unique modes of toxicological action. For example, the synthetic steroids EE2 and trenbolone bind to (and act as agonists of) vertebrate estrogen and androgen receptors, respectively, with similar or greater affinity than the natural endogenous hormones, estradiol and testosterone. In contrast, a variety of other medicinal pharmaceuticals are specifically designed to do the opposite, to be antagonists of these same receptors. As examples, tamoxifen (breast cancer treatment) and flutamide (prostate cancer treatment) bind quite specifically to vertebrate estrogen and androgen receptors, respectively, thereby blocking the activity of endogenous steroid hormones. But disruptors of the HPG axis are not limited to chemicals that bind directly to estrogen or androgen receptors; they also include chemicals that interact elsewhere in the overall biochemical pathway. As an example, there are chemicals that exert their activity through interactions with CYP (cytochrome

P450) enzymes involved in steroid production. The pharmaceutical chemical fadrozole acts to inhibit CYP19 aromatase, the enzyme that converts estradiol to testosterone. A number of conazole fungicides act as competitive inhibitors of several CYPs further up the steroid synthesis pathway (Ankley et al. 2005).

Unlike many other chemicals that have either non-specific (e.g., narcotics) or more generalized reactive modes of action (e.g., electrophilic chemicals interacting with nucleic acids and proteins), HPG-active compounds tend to have very specific interactions with particular molecular targets within the biochemical pathway. There are a number of consequences arising from this specificity. One important consequence of target specificity is potency. Many pharmaceuticals are designed to be highly specific, and thus are extremely potent. For example, EE2 and trenbolone affect reproduction and development in fish at water concentrations in the very low ng/L (part-per-trillion) range (e.g., Ankley et al. 2003; Länge et al. 2001), well below effect concentrations for most chemicals for which current ALC have been derived. These very low biologically-active concentrations present substantial challenges for analytical determinations associated either with lab-based effects testing or field monitoring of *in situ* exposures. In the case of EE2 and/or trenbolone, effects observed in fish are at concentration levels below the methodological limit of detection for most laboratories even in laboratory test water, and even more so ambient water and effluents.

Such high potency can influence how one would approach criteria derivation when the chemicals exert minimal acute toxicity, but cause mostly long-term, sub-lethal effects. Trenbolone and EE2 illustrate this situation quite well. Like most pharmaceuticals (some exceptions being chemotherapy and anti-parasitical agents), these chemicals are designed to "adjust" the biochemistry of the body without causing acute toxicity or other significantly adverse side effects. As a consequence, these types of pharmaceuticals tend to have low toxicity in short-term lethality assays (Webb 2001). In the context of criteria development, this has implications for the use of ACRs. Most conventional toxic pollutants with EPA ALC have ACRs of 10 or less (Cunningham et al. 2006; Host et al. 1995). In contrast, ACRs for EE2 and 17β-trenbolone in fish have been shown to range from 1,000 to greater than 300,000 (Ankley et al. 2005). Again, this is a result of relatively low acute toxicity and high chronic potency. Importantly, limited data for other MOA classes of pharmaceuticals suggest that this phenomenon is not restricted to endocrine-active substances. For example, Huggett et al. (2002) reported an ACR in fish of about 50,000 for propanolol, a β-blocker. As discussed in Section 2, this large difference in acute and chronic potency may both make CMC values moot in the environmental management of these chemicals, and introduce uncertainty in the extrapolation between acute and chronic effects in the derivation of a CCC.

The specificity of the molecular target also can greatly affect those taxa likely to be sensitive to the chemical MOA of concern. While some biological pathways (e.g., energy metabolism) tend to be highly conserved across all organisms, others can be quite specific to certain phylogenetic groups. Although the control of reproductive function through the HPG axis is highly conserved across vertebrate classes, lower taxonomic groups such as invertebrates have different endocrine system structure that function differently. For example, Segner et al. (2003) tested several estrogenic chemicals, including EE2, in a variety of partial and full life-cycle tests with a model fish (zebrafish) and several aquatic invertebrate species. They found that the fish was by far most

sensitive to the effects of the estrogenic chemicals, and was the only species that responded to EE2 at environmentally-relevant concentrations. As a result, it is likely that chronic toxicity data for fish would be the most influential in setting the criterion for EE2, and correspondingly unlikely that toxicological data for invertebrate species would have much impact. Plants do not have comparable endocrine system structure or function, and would not be expected to be sensitive to these types of compounds, but there is research that indicates that algal species may be a uniquely sensitive taxa for the assessment of other types of CECs such as antibacterial products like triclosan (Orvos et al. 2002; Wilson et al. 2003).

Specificity in MOA can also affect how or if effects are expressed within a toxicity test, even in potentially sensitive species. In the case of chemicals that affect endocrine function, there are distinct "windows" when animals are likely to be sensitive and/or exhibit adverse outcomes. For example, a popular amphibian early developmental assay-FETAX (Frog Embryo Teratogenesis Assay-*Xenopus*) would be inadequate for detecting thyroid-active toxicants because the period of exposure and observation occurs early in development before the thyroid axis is functional in *Xenopus*. In the case of HPG-active toxicants, there are two windows of sensitivity during an animal's life: during sexual differentiation in developing organisms (when "organizational" alterations occur), and during active reproduction in adults (when "activational" responses can be manifested; Ankley and Johnson 2004). As a result, it is critical that testing for HPG-active EDCs occur during periods when the system is vulnerable to disruption. It is equally critical that toxicity tests include observations during the periods when effects are expressed. Some of the changes caused during sensitive early developmental windows may not be expressed until later in life. For example, the ELS toxicity test protocol commonly used in criteria development to estimate the chronic sensitivity of fish contains the early life stages that could be sensitive to disruption of sexual development, but it does not extend through to maturation, and would therefore be insensitive for detecting disruption of sexual development.

3.2 Implications for ALC Development

As is clear from the text above, some characteristics of HPG-active chemicals (and many other CECs) create the need to carefully interpret the intent of the *Guidelines*, not just the routine derivation process. As indicated in Section 2.0 there is nothing about CECs that invalidates the principles embodied in the *Guidelines*; however, the *Guidelines* were written before many of the issues discussed in Section 3.1 were known, so they do not necessarily contain prescriptive guidance for some of the nuances created by some CECs. The following paragraphs discuss the implications of these issues for criteria development, following the four general topic areas outlined in Section 2.0:

- The need for and relevance of acute toxicity data and a CMC;
- Defining minimum data requirements in terms of taxonomic coverage;
- Defining appropriate chronic toxicity data; and
- Selecting effect endpoints upon which to base criteria

3.2.1 The Need For and Relevance of Acute Toxicity Data and a CMC

As described in Section 2.2, there are two primary uses for acute toxicity data under the *Guidelines*: 1) the derivation of the CMC; and 2) establishment of the CCC when the FAV/FACR method is used. As a practical matter, if the CMC is more than 96-fold higher than the CCC, then it will always be the CCC that is more limiting. This is because in the standard formulation of criteria, the CMC has a one-hour averaging period and the CCC a 96-hour averaging period; thus, if the difference between them is more than 96-fold, it is mathematically impossible to exceed the CMC without also exceeding the CCC. A minor exception to this issue occurs when ALC are implemented in an NPDES permit such that the CMC is applied to whole effluent while the CCC is applied after mixing, and the available in-stream dilution is large. However, these exceptions are rare, and even the 96-fold difference discussed here pales in comparison to the factors of 1,000 to 300,000-fold discussed previously in regard to EE2 and trenbolone. In cases where such extreme differences between acute and chronic toxicity thresholds exist, establishing ALC as having only a CCC seems a reasonable approach.

While it is easy to see why a CMC would not be necessary when you have sufficient acute test data to show that the CMC would be dramatically higher than the CCC, this begs the question of how much data are needed to decide that this is the case. This decision should occur during the "problem formulation" step in the risk assessment for a specific chemical/class, and should be guided by the following types of information:

- the amount and phylogenetic spread of acute toxicity data that are available;
- toxicity data from short-term exposures that do not meet the strict definitions in the *Guidelines* of acute toxicity data acceptable for criteria derivation, but from which information on responses to acute exposures can be inferred;
- short-term effect data garnered from longer-term exposures;
- information from closely related chemicals that are thought to have the same MOA, and have more robust acute data sets; and
- knowledge of the degree of phylogenetic distribution of the toxicity pathway of concern.

A complicating issue resulting from a "moot" CMC is that data availability for acute effects will likely be limited. As such, having less than the required acute MDRs may preclude the ability to derive a CCC using the FAV/FACR approach typically used in the *Guidelines*. For chemicals with highly specific modes of action and large ACRs (such as many EDCs), it is very likely that the mechanisms for acute and chronic toxicity differ, since biological activity resulting in chronic effects is designed into the product and not a secondary consequence - such as many of the historical contaminants for which EPA has developed criteria. Also, sensitivity of different taxa classes to acute and/or chronic toxicity varies widely due to presence (or absence) and structure and function of phylogenetically-conserved systems. Both of these issues would introduce considerable uncertainty into the availability and interpretation of ACRs, and probably make it inadvisable to use the FAV/FACR approach anyway. The *Guidelines* discuss the inadvisability of using the ACR approach when ACRs vary by more than a factor of 10 without a clear relationship to taxonomy or acute sensitivity (page 41 of the *Guidelines*). A more advisable approach would generally be to develop a CCC directly from a sufficiently robust set of chronic data, using the procedures outlined in the *Guidelines* or an appropriate modification thereof.

3.2.2 Defining Minimum Data Requirements in Terms of Taxonomic Coverage

To develop a CCC directly from chronic toxicity data (rather than via FAV/FACR), the *Guidelines* require that acceptable chronic toxicity data be available from at least eight families with a taxonomic distribution fulfilling the requirements specified in the *Guidelines* (referred to as the "minimum data requirements" or "MDRs"). Having a blanket requirement for meeting the eight MDRs was included to insure a minimum level of "certainty" that the *Guidelines* will be protective of the broad phylogenetic distribution of organisms found in aquatic systems. Including this phylogenetic spread also enables criteria to be developed for chemicals for which the toxicological MOA is not known. Instead of "knowing" what organisms are most likely to be sensitive to a particular chemical, requiring a broad spread of empirical toxicity data makes it likely that whatever taxa may be sensitive to a chemical, they will be represented to some degree in the toxicity data set.

In the case of EDCs, PPCPs, and certain other chemical classes, we may have a reasonable understanding of the toxicological MOA for the chemical, and from that knowledge we may be able to infer what taxa are most likely to be sensitive to a particular chemical (Ankley et al. 2007; Williams 2005). As discussed in Section 2.2, the procedure used in the *Guidelines* for estimating the 5^{th} percentile of a toxicity distribution is dependent on only the four lowest values; for this reason exact values for insensitive genera are not necessary, as long as there are sufficient data to infer that their sensitivity is lower than the four most sensitive genera.

So how does one determine that a particular taxon is insensitive? The general structure of the *Guidelines* presumes that sensitivity is determined by conducting an acceptable toxicity test with that taxon. However, one can infer that the actual need is only to have sufficient information to conclude that the taxon is insensitive; if that determination can be confidently made based on other information, the information need may be met even if an actual toxicity test with that particular organism and chemical has not been conducted. This does not change the intent of the *Guidelines*. It only acknowledges the possibility that there is more than one way to meet the information requirement.

Using the example of EE2, there is both physiological understanding and some empirical toxicity data to support the belief that vertebrates will be far more sensitive to EE2 toxicity than will invertebrates (see Part II of this white paper and Segner et al. 2003). As such, it would seem inappropriate to invest resources in testing a wide range of invertebrate taxa classes for sensitivity when all existing data indicate that the data would not affect the final criterion, which would be driven by sensitivity of vertebrates. In this case, it makes sense to argue that certain of the eight MDRs might be declared met not through direct testing, but through toxicological understanding of the chemical's MOA and the physiology of those other taxa or existing toxicity data that establishes sensitivity differences among taxa.

While this logic is clear, one must be careful in presuming that the primary MOA demonstrated by organisms with the target physiology is the only toxic MOA for the chemical. Particularly given the phylogenetic diversity of organisms, it is always possible that a chemical that behaves

with one MOA in one class of organisms may exert toxicity through a different mechanism in a different phylogenetic group. There are precedents for this scenario (Ankley et al. 2007). For example, exposure to the non-steroidal anti-inflammatory drug diclofenac via consumption of dead livestock has greatly diminished some populations of vultures in several East Asian countries. Diclofenac kills the birds through renal failure, which is only a relatively minor side-effect of the drug in mammals. While the mechanism of renal toxicity in vultures is likely molecularly related to the mechanism of therapeutic action in man, i.e., both seem to occur due to inhibition of prostaglandin synthesis (Meteyer et al. 2005), the inhibition of similar molecular components appears to be manifested as dramatically different whole organism endpoints. The key is in achieving a reasonable balance between expending resources on collecting data most likely to influence the criterion, while maintaining some kind of backstop against initially unexpected toxicity in other organisms.

One possibility for enhancing confidence regarding phylogenetic sensitivity is in considering data for other, closely-related chemicals with the same MOA. While the *Guidelines* focus analysis on toxicity data for the specific chemical in question, an understanding of toxicological MOA can also lead to an understanding of how other chemicals might act to exploit the same biological system in the same way. For example, one might reasonably infer that the relative species sensitivity to EE2 is likely similar to 17-ß estradiol (E2), the natural hormone which EE2 mimics. If, for example, there were a taxon which had been tested and found insensitive to E2, but had not been tested with EE2, it seems a reasonable assumption that that taxon would also be insensitive to EE2.

The possibility of fulfilling certain information requirements using data other than from direct toxicity testing does raise some other interpretation challenges, in particular the definition of the sample size for determining the 5^{th} percentile of the genera sensitivity distribution. For example, if one has reason to believe that all crustaceans would be insensitive to a chemical, how many genera does that assertion represent in the calculation of the genera sensitivity distribution? While this is a real issue that will have to be addressed, we believe the problem is tractable and the details of the resolution are left to later work.

Because of the risk that our mechanistic understanding of a chemical may be incomplete, it seems unlikely that one could justify completely bypassing several MDRs solely on theoretical arguments (e.g., developing a criterion for a testosterone mimic based only on chronic toxicity data for vertebrates, with no invertebrate data at all). At the same time, prudent application of other data types to fulfill certain information requirements for criteria derivation does seem appropriate. Given the tremendous variation in understanding and availability of data likely to exist for different CECs, it is presumed that at least initial application of this approach will have to be justified on a chemical-by-chemical basis using appropriate scientific judgment. However, lines of evidence that might be applicable to this determination include:

- an in-depth understanding of the toxicological (or, in the case of drugs, therapeutic) MOA;
- information on the basic physiology of other taxa in relation to the MOA;
- toxicity data from chronic exposures or other relevant experiments that do not meet the strict definitions of acceptable chronic data given in the *Guidelines*, but from which

information on relative taxon sensitivity can be inferred; and
- information from closely related chemicals that are thought to have the same MOA and have more robust acute or chronic data sets.

A separate, but related issue arises in respect to data from species not resident to North America. The *Guidelines* specify the use of toxicity data only from species resident to North America. However, particularly in regard to the study of EDCs, some fish species not resident to the U.S. have been advanced as experimental models for the evaluation of the chronic effects of EDCs to fish. Two clear examples at the time of this report are the zebrafish (*Brachydanio rerio*) and the Japanese medaka (*Oryzias latipes*), for which equivalency of EDC test data (with the fathead minnow) has been proposed through international groups such as the Organization for Economic Cooperation and Development (OECD; Ankley and Johnson 2004). These species have a rich toxicological database, and we know of no reason to believe that their sensitivities would be expected to be substantively different from sensitivities of at least some fish resident to the U.S. In keeping with international harmonization, we suggest that toxicity data from species with recognized international equivalency be included in criteria derivation with the full weight given to data from resident species.

3.2.3 Defining Appropriate Chronic Toxicity Data

The *Guidelines* state that acceptable chronic tests for criteria derivation are full life-cycle exposures (F_0 egg to F_1 offspring) for both vertebrates and invertebrates, as well as partial life-cycle (adult to juvenile) and early life-stage (ELS; egg to juvenile) tests for fish. The acceptance of ELS tests in particular as acceptable chronic tests is predicated on the work of McKim et al. (1978) and other evidence that the toxicity thresholds obtained from ELS tests are generally within a factor of two of the thresholds from life-cycle chronic tests.

While this general approach has been applied with apparent success for many chemicals, the *Guidelines* intimate concerns with the approach, noting that for some chemicals, ELS tests might not be good predictors of chronic toxicity, which would violate the principle underlying the use of ELS tests as chronic data (page 39 in the *Guidelines*). As noted previously, toxicological data for chemicals like EE2 show that certain chemicals may have potent effects on life processes that lie outside the exposure period represented by ELS tests (e.g., pronounced effects on reproduction), or on life processes for which the expression of effects does not occur until after the ELS period (e.g., embryo or larval exposure resulting in effects on sexual development and maturation in adult fish; see Section 3.1). It is clear from these examples that there are chemicals for which ELS tests should not be used as surrogates for full life-cycle exposures. In fact, chemicals that affect sexual differentiation may not be adequately assessed even with partial life-cycle exposures, since these protocols do not generally include observation of sexual development/maturation in fish exposed during early development.

While the "Good Science" clause and other text in the *Guidelines* would not support reliance on ELS tests as chronic data for chemicals known to have specific effects on other life processes, such as sexual development or reproduction, the *Guidelines* would allow the development of a criterion using only ELS data for fish if there were not any specific data to indicate that this approach would be inappropriate. This is akin to an "innocent until proven guilty" approach.

However, we believe experiences with chemicals like EDCs make clear the need to move from the previous approach to one of "guilty until proven innocent." In other words, it is probably wiser to require that the chronic toxicity data for fish include exposure and observation over a full life-cycle unless there is an affirmative reason to believe that it is not necessary (note: this issue is equally relevant to invertebrates species, but the ELS tests discussed in the *Guidelines* are focused explicitly on fish; invertebrate tests would already be required to be life-cycle). In keeping with this shift in emphasis, we believe the requirements for chronic toxicity data in the *Guidelines* should be tightened by adding the further requirements that either:

1) Full life-cycle data be available for at least one fish species; or

2) There is a body of experimental information indicating that life processes outside the ELS or partial life-cycle exposure/observation windows would not be important to capturing the important toxicological effects of the chemical.

At first glance, #2 may seem like requiring the proof of a negative, in that one would have to actually conduct the life-cycle test required by #1 in order to show that #2 is true. However, we believe there may be circumstances in which there may be data that speak to the sensitivity of different life stages that come from studies that, while scientifically valid, for some reason do not meet all the requirements of a valid life-cycle test as defined in the *Guidelines*. For example, there may be data for a life-cycle test with a non-resident species that includes the relevant life processes but does not qualify as an acceptable chronic test for the derivation of criteria because it is non-resident. Alternatively, there may be data from experiments that violate other requirements of acceptable toxicity data under the *Guidelines*, but still provide insight into sensitive exposure periods or life processes. Even though CVs from such data may not be used directly to calculate a chronic criterion, it seems reasonable to use such data to evaluate the question of where in the life-cycle there are important windows of exposure and/or effect and how that constrains the adequacy of ELS tests to represent chronic toxicity. In other cases, there may be sufficient information from other types of research to demonstrate to a reasonable level of certainty that a chemical's toxicological mechanism(s) would not preclude the use of ELS tests as indicators of chronic toxicity.

Where life-cycle toxicity data are available, the results of those experiments should be carefully examined to determine the likelihood that important windows of exposure or effect lie outside ELS test protocols. Obviously, if there is meaningful potential for effects outside the ELS exposure period, ELS tests should not be used as surrogates for more involved chronic tests. It may also be that the knowledge of toxicological mechanism for a particular chemical may be sufficient that meaningful chronic toxicity data could be developed from exposures that have a structure different from the life-cycle, partial life-cycle, and ELS protocols defined explicitly in the *Guidelines*. While defining such alternate protocols is beyond the scope of this document, we recognize the potential for such a situation and leave it to appropriate implementation of the "Good Science" clause to allow for inclusion of such alternative exposure protocols as surrogates for chronic toxicity data, most likely in addition to, rather than instead of, data from life-cycle toxicity tests.

At the other end of the spectrum lie toxicity tests that extend beyond the definition of a full life-

cycle test, often referred to as multi-generational tests. Because they encompass the full range of life processes as a life-cycle test, we feel that they should be included as acceptable chronic tests, assuming they meet all other requirements for test acceptability. Some studies have reported effects from EDC or other chemicals in which exposure to one generation creates effects in a later generation that were not observed in prior generations even at the same life stage (Nash et al. 2004). If substantial, such effects could create a situation where even full life-cycle toxicity tests might underestimate the chronic toxicity of a chemical and therefore produce criteria that are potentially under-protective. While we recognize the potential for this situation, at present we believe there is not sufficient reason to make multi-generational testing a requirement for criteria development, unless there is specific, compelling information that a criterion would be substantially under-protective if multi-generational effects were not rigorously considered.

3.2.4 Selecting Effect Endpoints Upon Which to Base ALC

The selection of endpoints appropriate to the derivation of ALC must be tied to the narrative intent of the overall *Guidelines*. The stated goal of ALC is to "protect aquatic organisms and their uses" (see *Water Quality Standards Handbook*; U.S. EPA 1994b). While the exact meaning of "protection" is not defined, there is considerable discussion in the *Guidelines* document that makes clear that protection does not mean the prevention of any measurable biological effect in any organism. Instead, there is discussion of endpoints that are "biologically important" and prevention of "unacceptable effects"; this implies that in the context of criteria there are effects that are "biologically unimportant" and/or levels of effect that are "acceptable." Related concepts include the idea that natural populations can withstand some magnitude/frequency of disturbance and still meet the intent of the *Guidelines*.

With "protection of aquatic organisms and their uses" as the assessment endpoint, a decision must be reached as to which biological responses (measurement endpoints in risk assessment parlance) are appropriate to address this goal. Survival, growth, and reproduction are processes that are generally accepted as being directly related to this goal, as these are all demographic parameters that directly affect population dynamics (although, the exact quantitative relationship is not always fully determined). However, there are many more biological responses that have been observed in response to toxicant exposure, both at the whole organism level (e.g., behavior) and at lower levels of biological organization (e.g., biochemical or histological changes). For many of these endpoints, their relationship to the assessment goal, "protection of aquatic organisms and their uses," is less clear. In this regard, we must consider an additional goal of the *Guidelines* – that criteria "provide a reasonable and adequate amount of protection, with only a small possibility of considerable overprotection or under-protection" (page 5 of the *Guidelines*). In keeping with this intent, it is important that criteria focus on endpoints that affect the assessment endpoint, but not create overprotection by preventing any measurable effect (or possibility of that effect). There must be a reasonable, affirmative connection between the measured response and the assessment endpoint.

The Agency's *Framework for Ecological Risk Assessment* (U.S. EPA 1992) identifies this problem:

> *In many cases, measurement endpoints at lower levels of biological organization may be more sensitive than those at higher levels. However, because of compensatory mechanisms and other factors, a change in a measurement endpoint at a lower organizational level (e.g., a biochemical alteration) may not necessarily be reflected in changes at a higher level (e.g., population effects).* (p. 14)

And later on:

> *Ideally, the stressor-response evaluation quantifies the relationship between the stressor and the assessment endpoint. When the assessment endpoint can be measured, this analysis is straightforward. When it cannot be measured, the relationship between the stressor and measurement endpoint is established first then additional extrapolations, analyses, and assumptions are used to predict or infer changes in the assessment endpoint.* (p. 23)

> *Measurement endpoints are related to assessment endpoints using the logical structure presented in the conceptual model. In some cases, quantitative methods and models are available, but often the relationship can be described only qualitatively. Because of the lack of standard methods for many of these analyses, professional judgment is an essential component of the evaluation. It is important to clearly explain the rationale for any analyses and assumptions.* (p. 23)

Existing criteria documents contain many types of data that were not used in the criteria derivation (the documents collate and review these data, but they are not used to actually define the criterion concentration) and it is useful to the discussion here to consider how such data have been interpreted. For example, the following text is derived from the most recent criteria document for ammonia (U.S. EPA 1999, see Appendix 5):

> *Endpoint indices of abnormalities such as reduced growth, impaired reproduction, reduced survival, and gross anatomical deformities are clinical expressions of altered structure and function that originate at the cellular level. Any lesion observed in the test organism is cause for concern and such lesions often provide useful insight into the potential adverse clinical and subclinical effects of such toxicants as ammonia. For purposes of protecting human health or welfare these subclinical manifestations often serve useful in establishing 'safe' exposure conditions for certain sensitive individuals within a population.*

> *With fish and other aquatic organisms the significance of the adverse effect can be used in the derivation of criteria only after demonstration of adverse effects at the population level, such as reduced survival, growth, or reproduction. Many of the data indicate that the concentrations of ammonia that have adverse effects on cells and tissues do not correspondingly cause adverse effects on survival, growth, or reproduction. No data are available that quantitatively and systematically link the effects that ammonia is reported to have on fish tissues with effects at the population level. This is not to say that the investigators who*

reported both tissue effects and population effects within the same research did not correlate the observed tissue lesions and cellular changes with effects on survival, growth, or reproduction, and ammonia concentrations. Many did, but they did not attempt to relate their observations to ammonia concentrations that would be safe for populations of fish under field conditions nor did they attempt to quantify (e.g., increase in respiratory diffusion distance associated with gill hyperplasia) the tissue damage and cellular changes (Lloyd 1980; Malins 1982). Additionally, for the purpose of deriving ambient water quality criteria, ammonia-induced lesions and cellular changes must be quantified and positively correlated with increasing exposures to ammonia.

In summary, the following have been reported:

1. Fish recover from some histopathological effects when placed in water that does not contain added ammonia.

2. Some histopathological effects are temporary during continuous exposure of fish to ammonia.

3. Some histopathological effects have occurred at concentrations of ammonia that did not adversely affect survival, growth, or reproduction during the same exposures.

Because of the lack of a clear connection between histopathological effects and effects on populations, histopathological endpoints are not used in the derivation of the new criterion, but the possibility of a connection should be the subject of further research.

As discussed in greater detail below, chemicals such as EDCs have been shown to produce a wide variety of measurable changes at many different levels of biological organization. The challenge is to select from among those the endpoints that have sufficiently clear connection to expected effects on populations of aquatic organisms.

3.2.4.1 Specific Examples of Measurable Changes at Different Levels of Biological Organization

The range of organismal endpoints that have been reported in the literature is vast, and varies to some degree on the organism and toxicant. With respect to only the HPG axis in vertebrates, this range of endpoints over and above direct measures of survival, growth, and reproduction includes:

- Biochemical measures (e.g., the female-specific yolk precursor protein vitellogenin; native hormones estradiol, testosterone, 11-ketotestosterone);
- Histopathological measures (e.g., proportion of spermatogonia, presence of testis-ova, oocyte atresia, Leydig cell hyperplasia/hypertrophy);

- Gross morphology (e.g., secondary sex characteristics: nuptial tubercles, coloration, ovipositors); and
- Behavioral measures (e.g., nest building, defense/aggression).

A comprehensive survey and evaluation of all such endpoints is far beyond the scope of this document. In lieu of that, this section presents in depth discussion of several individual measures relevant to the HPG axis, including their strengths and weaknesses as direct indicators of likely population level effects. The point of this discussion is simply to provide examples of the issues that must be considered in making a decision as to the biological importance and scientific defensibility for a specific endpoint, organism, or toxicant as it pertains to ALC derivation. These decisions will likely require case by case consideration; in certain circumstances, the suitability of a particular endpoint may vary across chemicals depending on how an individual chemical influences that endpoint.

One of the challenges that arises when incorporating alternative endpoints into criteria derivation is the need to not only conclude that the endpoint warrants consideration, but also establish some definition of what level of effect on that endpoint is unacceptable. While these links may not be completely quantitative, one would not want the definition of an unacceptable effect on one endpoint to be grossly disproportional to that considered unacceptable for another (i.e., if a 20% reduction in reproduction is considered unacceptable, what degree of estradiol (E2) suppression is equivalent to a 20% reduction in reproduction?).

In the text that follows, endpoints are categorized as being either "organizational" or "activational." Organizational endpoints are those that are a result of changes to the normal growth and development of an organism, and are generally not reversible with cessation of exposure. Activational endpoints are those that occur in comparatively plastic tissues in response to exposure, but which may revert to their prior or normal condition with cessation of exposure.

Organizational Endpoint: Sex Reversal

Exposure of developing fish to endocrine-active materials during sensitive "windows" in early development can skew phenotypic sex dramatically toward either females (estrogenic chemicals) or males (androgenic chemicals). This response has been exploited by aquaculturists, who for many years have used potent natural or synthetic steroids to produce mono-sex stocks. The sensitivity of fish to this type of "sex reversal" is species-specific, and critical windows of exposure can vary markedly across species. The response can be manifested in several different ways, ranging from more or less completely sex-reversed animals (i.e., occurrence of gonads and secondary sex characteristics completely reflective of the opposite sex) to more subtle changes, such as the occurrence of intersex gonads (discussed further below). A significant challenge in assessing this condition-either in the lab or field-is knowledge of actual genetic sex of the fish. Since the molecular basis of sex determination in many fish is not known, reliable genetic markers of what sex an animal is programmed to be are not available for most test species (one notable exception here is the Japanese medaka, which is commonly used for endocrine testing in some parts of the world; Ankley and Johnson 2004). The net result of this is that the only way to practically monitor sex reversal in most fish species is indirectly, through analysis of sex ratios (generally based on phenotypic sex). This requires, of course, considerable background

knowledge concerning "normal" sex ratios for a species (or even strain) of fish. For some lab test species (e.g., fathead minnow), the normal sex ratio appears to be about 1:1, while for other commonly-tested small fish models (e.g., zebrafish), the ratio can be quite variable (Ankley and Johnson 2004). In field studies, collection of accurate sex ratio data also can be exceedingly difficult, depending on variables such as sampling gear and location and timing of collections.

Changes in the sex ratio of populations of fish, either in the lab or field, can be quite indicative of an endocrine-specific MOA, indicating exposure to estrogenic or androgenic chemicals (or even chemicals that block the actions of sex steroids). Significantly, from a risk assessment perspective, alterations in sex ratio could also have direct implications for spawning success and population viability. The degree to which sex ratios are critical in determining embryo production will vary based on reproductive strategies of the species of concern (e.g., broadcast versus paired spawners); however, from an evolutionary perspective, one would speculate that any departure from normal sex ratios for a species/population might be considered maladaptive.

Organizational Endpoint: Intersex

Exposure to certain classes of endocrine-active chemicals during critical windows in early development can produce intersex gonads (commonly termed testis-ova), a situation in which the gonads simultaneously contain both ovarian and testicular tissue. Different studies from around the world have shown an elevated occurrence of intersex fish downstream of municipal effluents containing natural and synthetic steroidal estrogens, including EE2 (WHO 2002). In fact, collection of intersex fish from the field has been one of the most visible manifestations of the effects of EDCs on fish/wildlife. For example, in a widely publicized USGS study, Blazer et al. (2007) recently reported that in the South Branch of the Potomac River and select nearby drainages, more than 80 percent of all the male smallmouth bass sampled had oocytes growing within their testicular tissue. Although histology is required to determine and quantify intersex, the techniques involved are relatively straight-forward. What is more challenging than measurement is interpretation of the results. For example, it appears that some degree of background intersex can occur, even in species held under carefully-controlled conditions (Grim et al. 2007). The degree of background intersex and sensitivity to chemically-induced intersex appear to be quite species-specific, requiring a thorough understanding of normal gonad differentiation and development in the species of concern.

Even in species for which background intersex is low, there is uncertainty as to the degree to which the condition could occur and not interfere with normal reproductive function. For example, in a field study in the UK, Jobling et al. (1998) noted a wide range of intersex in roach collected, even from the same site, with severity of the response ranging from occurrence of a few primary oocytes in otherwise normal testicular tissue to instances where there was a complete absence of sperm ducts in the males. Arguably, the former fish could produce viable sperm, while the latter certainly would not. So, although intersex is an intuitively reasonable endpoint upon which to base predictions of possible adverse effects of endocrine-active chemicals on reproductive success, determination of the relationship between severity of the condition and production of viable embryos is required to conduct this analysis.

Activational Endpoint: Behavior

Although not usually considered a biomarker in the traditional sense, behavior is an endpoint that historically has been seldom used for ecological risk assessment, including the derivation of ALC. There are several reasons for this: (1) the types of assays used to assess behavior can be quite labor-intensive, (2) many methods for assessing toxicant-induced behavior have some degree of subjectivity, (3) many behavioral changes (e.g., gill ventilation in fish) are relatively non-specific in that they do not necessarily reflect exposure to chemicals with a specific MOA, and (4) translation of behavioral changes into adverse effects on endpoints such as survival, growth and reproduction can be difficult. Nonetheless, virtually all environmental toxicologists recognize the potential for chemically-induced alterations in behavior to influence the health of individual animals and populations.

There are some compelling reasons to consider behavior as a potentially useful/important endpoint in assessing the ecological risk of certain classes of endocrine-active chemicals. First, estrogens and androgens are known to play relatively specific roles in a variety of reproductive behaviors in fish, including competition for mates, courtship and nest-holding/guarding. Alterations in any of these behaviors theoretically could affect reproductive success and, hence, population status. In recognition of this there have been several recent papers describing straight-forward, relatively quantitative assays for assessing the effects of endocrine-active substances on fish reproductive behavior. For example, Martinovic et al. (2007) conducted a study in which they showed that male fathead minnows exposed to a relatively low concentration of 17β-estradiol, and subsequently placed in a competitive spawning situation with non-exposed males, failed to compete successfully for nesting sites/females. Similar types of results have been reported for other fish species exposed to steroidal estrogens (e.g., EE2; see Part II of this white paper), suggesting that behavioral alterations could be important to consider, especially if they occur at exposure concentrations below those that cause effects on more traditional endpoints such as development and egg production.

Activational Endpoint: Secondary Sex Characteristics

As described above, exposure of developing animals to endocrine-active chemicals can alter phenotypic sex, resulting in skewed sex ratios in populations. These organizational changes observed in secondary sex characteristics (in sexually dimorphic species) and/or gonads typically are not reversible. However, it also is possible to alter secondary sex characteristics, usually in a reversible manner, in sexually-mature fish through exposure to endocrine-active substances. For example, estrogens or anti-androgens can reduce expression of androgen-dependent secondary sex characteristics in males. Similarly, androgenic chemicals can cause female fish to develop male secondary sex characteristics, such as nuptial tubercles in the fathead minnow or elongated anal fins in the Japanese medaka (Seki et al. 2006). Alterations in secondary sex characteristics are much less useful indicators of endocrine-mediated responses in test species, such as zebrafish, with limited sexual dimorphism (Seki et al. 2006).

Alterations in secondary sex characteristics in adult fish can, in some instances, be subtle and somewhat subjective with respect to interpretation. For example, reductions in the status of

existing structures in fish (such as nuptial tubercles in male fathead minnows or anal fin length in male medaka) can be difficult to quantify. However, when there is a *de novo* synthesis of structural characteristics where none previously existed (such as tubercles in female fathead minnows), the response is not only quite specific (in this case to an androgenic MOA), but very easy to detect (i.e., the baseline, control condition is zero).

Although changes in secondary sex characteristics appear to be reasonable mechanistic biomarkers for some endocrine MOA, their utility as a predictor of adverse outcomes (e.g., egg production) is uncertain. Specifically, given our current understanding of fish reproductive physiology/endocrinology, causative links between secondary sex characteristics and gamete quality would be difficult to define. At best, a correlative association may be identified between the two parameters. For example, in studies with the synthetic androgenic steroid 17β-trenbolone, egg production appeared to be reduced at about the same test concentration that caused some degree of nuptial tubercle formation in females (Ankley et al. 2003).

Activational Endpoint: Vitellogenin

Vitellogenin status is probably the most commonly measured endpoint in studies with endocrine-active chemicals in fish. Measurement of the lipoprotein (or its mRNA) is relatively easy via a variety of methods (although most techniques have some degree of species specificity; Wheeler et al. 2005). Production of mRNA (*vtg*) and protein (VTG) in the liver of female oviparous (egg-laying) vertebrates is normally stimulated by activation of the estrogen receptor by endogenous estradiol. The protein is released to the plasma and subsequently deposited in the ovary where it forms a key constituent of developing oocytes. VTG levels in male oviparous animals typically are non-detectable due largely to very low circulating estradiol concentrations; however, males retain the molecular "machinery" in the liver necessary to produce VTG. Hence, exposure to even relatively low amounts of exogenous estrogen or estrogen mimics can stimulate a marked induction of VTG in males. The response not only is specific and sensitive (in part due to a baseline of essentially zero), but relatively sustained after exposure, as the males have no mechanism whereby to clear the protein from their blood.

Although *vtg* and/or VTG induction in male fish is an excellent biomarker of exposure to estrogens (Lattier et al. 2002), the response appears to have little direct (i.e., causative) value in terms of predicting adverse effects on reproduction (e.g., Wheeler et al. 2005). This perhaps should not be surprising given that VTG production in males is not part of any normal physiological pathway. It is possible, however, that correlative relationships between *vtg* and VTG induction in males by exogenous estrogens (such as EE2) and overall effects on fish population status could be derived (e.g., Kidd et al. 2007). This certainly merits additional study, but at present, it appears that the most technically-defensible use of VTG occurrence in male fish is as an indicator of exposure to estrogenic substances in the field and/or confirmation of chemical MOA in laboratory studies.

As opposed to males, VTG has a clear physiological role in females in that the protein is essential to egg production. Concentrations of VTG in females can be reduced by endocrine-active chemicals that directly or indirectly inhibit steroid (ultimately estradiol) production. For example, aromatase inhibitors such as some conazole fungicides decrease steroid production by

inhibiting enzymes involved in steroidogenesis, while other androgenic chemicals like trenbolone decrease steroid production through feedback inhibition in the HPG axis. As a consequence, these classes of endocrine-active chemicals reduce normal VTG production in female fish, thereby reducing fecundity and, ultimately, affecting population status (Miller et al. 2007). Therefore, in the case of females, VTG status may be effectively used as a biomarker both of exposure and effects. Kidd et al. (2007) found that VTG was elevated in female fathead minnows outside of their spawning season. Therefore, elevated VTG in females outside of the spawning season may also be an important measure of stress.

3.3 Pathways and Receptors Beyond the HPG-Axis

As was explained at the outset, this section (Section 3) has a substantial focus on the HPG-axis not because it is the only MOA that is of concern in this document, but because it is currently prominent in both social and scientific arenas. However, it is important to re-emphasize that the use of HPG-active chemicals as a basis for discussion does not imply that this is the only group of CECs of concern with respect to the development of ALC, or the only group for which there may be need for supplementation of the explicit procedures outlined in the *Guidelines*.

As an example, the hypothalamic-pituitary-thyroid (HPT) axis is another endocrine system present in vertebrates that governs important biological pathways and is potentially subject to disruption. Similar to the role of steroid hormones in the HPG axis, actions of the HPT axis are mediated through thyroid hormone, which is involved in the regulation of metabolic activity, energy consumption and muscular activity in adult animals, and the regulation of postembryonic or perinatal growth and development in developing animals, especially in the central nervous system (Chatterjee and Tata 1992). Thyroid hormone is also responsible for the obligatory induction and maintenance of metamorphosis in amphibian and other poikilotherms, and may also play a role in male reproduction (Peterson et al. 1997). Since the actions of thyroid hormone are mediated via binding to highly-conserved nuclear thyroid hormone receptors and modulating transcription of specific genes, disruption of the HPT axis can be disrupted in many ways parallel to those discussed for the HPG axis (Farwell and Braverman 2006), and in doing so, create similar challenges for the development of ALC. Only a few of the developmental actions of thyroid hormones, however, are the result of the direct interaction of the hormone and receptor. Instead, most are indirect via the influence of thyroid hormone on other hormone or growth factors. For example, some of the growth-promoting effects of thyroid hormones on juveniles are indirectly mediated via growth hormone released from the pituitary gland (Chatterjee and Tata 1992).

The amphibian metamorphosis assay is one of the thyroid-relevant *in vivo* screening assays EPA has developed to detect chemicals that interfere with the thyroid hormone system. The assay represents a generalized vertebrate model to the extent that it is based on the conserved structure and functions of the thyroid systems, and thus mirrors some of the assays developed and discussed earlier for the HPG axis. This particular assay is important because amphibian metamorphosis provides a well-studied, thyroid-dependent process which responds to substances active within the HPT axis (Fort et al. 2007). The utility of this and other similar HPT-specific assays for development of ALC is predicated on the principle that the dramatic morphological

changes that occur during post-embryonic development of vertebrates are dependent on the normal function of the HPT axis, and that interference with this process leads to quantifiable effects (Zoeller and Tan 2007).

Other pathways relevant to this discussion could include any of a number of those regulated by different nuclear hormone-type transcription factors, such as the progesterone, glucocorticoid and aryl hydrocarbon (Ah) receptors. Of these the Ah receptor is of particular interest because it has been well studied and is key to the toxicity of several important environmental contaminants such as dioxins and PCBs. Ah receptor agonists are extremely toxic to early life stages of some vertebrates species (e.g., adult fish are at least 10 times less sensitive than early life stages), can induce delayed mortality not captured in short-term (e.g., 96-hour) toxicity tests, and are not very toxic to invertebrates, which lack the receptor (Cook et al. 1993; Mount et al. 2003; Tanguay et al. 2005). Hence, as is true for HPG-active chemicals, knowledge that a contaminant may be an Ah receptor agonist can help focus testing to determine ecological risk (Cook et al. 1993).

Although the previous systems are generally found in vertebrates but not invertebrates, parallel developmental, reproductive, and homeostatic systems exist in invertebrates (Lintelmann et al. 2003) and are most likely just as susceptible to disruption by xenobiotic chemicals. In fact, many pesticides are designed explicitly to disrupt biochemical pathways specific to invertebrates or sub-groups of invertebrates as a means to reduce effects on non-target (vertebrate) organisms. Some endocrine-mediated processes unique to certain taxa of invertebrates include molting, limb generation, diapause, pheromone production, pigmentation and coloration, and metamorphosis. For these processes, the most important endocrine regulators in arthropods are ecdysone and related compounds (ecdysteroids), which are involved in embryonic development, molting, metomorphosis, reproduction, and pigmentation (Lintelmann et al. 2003). Juvenile hormones in insects and methylfarnesoate in crustaceans (both belonging to the class of sexual hormones called terpenoids) are also deemed necessary to mediate the regulatory functions of ecdysteroids (DeFur et al. 1999). Research on the effects of CECs on these systems is still in its early stages, but the parallels with other systems that are susceptible to disruption are clear, and may therefore create similar issues for the development of ALC.

4.0 SUMMARY AND RECOMMENDATIONS

Through its deliberations, the workgroup concluded that the basic framework and conceptual underpinnings of the *Guidelines* apply to CECs as well as other chemicals. Further, the "Good Science" clause of the *Guidelines* provides the flexibility to adopt procedures that will produce a technically rigorous and protective criterion. The focus of this report has been the interpretation and adaptation of the principles set forth in the *Guidelines* with respect to common toxicological characteristics of CECs. In that regard, the workgroup identified a number of possible modifications or alternate interpretations that might aid those developing criteria for CECs to do so in a resource efficient manner that takes best advantage of existing knowledge.

Although some of the recommendations involve increasing flexibility in meeting certain data requirements, the intent is to guide the generation of ALC for CECs that have the same technical rigor as 304(a) criteria developed for other chemicals; these are not methods for "short-cut" criteria. This is a significant point, because an important feature of the *Guidelines* is defining a minimum technical rigor that criteria must have; if insufficient information exists to achieve a minimum level of confidence in the calculated criterion, then criteria should not be derived. The important consequence of this for risk assessors and managers is that when criteria are used to make regulatory decisions, one can have confidence that uncertainty regarding the criterion is not excessive. In other words, criteria derived using the *Guidelines* are often used as both "walk away values" (i.e., there is high confidence that there is little or no risk when exposures are below criteria) and as indicators of risk (implying that effects are likely when criteria are exceeded). If greater uncertainty were allowed in criteria, then the ability to use the values in this way would be compromised.

A negative aspect to establishing a minimum level of information for criteria is that there may be chemicals for which regulatory guidance is needed, but for which toxicological data are insufficient to meet the minimum standards of the *Guidelines*. In such cases, there may still be a need for alternate approaches to derive interim regulatory guidance values on which to base decisions that must be made before sufficient information for a complete water quality criterion can be gathered. While much of the discussion in this report might be useful to inform the development of such an approach, it must be emphasized that developing procedures to derive interim regulatory guidance values based on limited toxicity information is a separate matter and would require considerable additional analysis.

The subsequent sections summarize the issues and recommendations of the workgroup according to the areas of concern identified above.

4.1 Relevance of Acute Toxicity Effect Levels in Setting ALC for CECs

Some CECs may not be acutely toxic, or may only be acutely toxic at environmentally irrelevant concentrations. Thus, if the minimum data requirements for acute toxicity data are not already met by existing data, conducting additional acute tests might be unwarranted. Indication of lack

of acute toxicity in key aquatic species might also warrant direct calculation of the CCC rather than using the FAV/FACR approach, and thus eliminate the need for the full suite of acute toxicity tests normally required.

For a CEC of interest, available information should be reviewed to determine if the CMC would be sufficiently higher than the CCC such that developing the CMC is not needed. Exactly how much data is a risk management judgment, and probably does not have a unique answer. We recommend that the following information be considered when addressing this issue:

- the amount and phylogenetic spread of acute toxicity data available;
- toxicity data from short-term exposures that may not meet the strict definitions in the *Guidelines* of acute toxicity data acceptable for criteria derivation, but from which information on responses to acute exposures can be inferred;
- data on short-term exposures garnered from longer-term exposures;
- information from closely related chemicals thought to have the same MOA that have more robust acute data sets; and
- knowledge of the degree of phylogenetic distribution of the toxicity pathway of concern.

4.2 Defining Minimum Data Requirements in Terms of Taxonomic Coverage

One consequence of dropping acute testing requirements in criteria derivation is the inability to calculate a CCC using the ACR approach, i.e., as the quotient of the FAV and FACR. In addition, for chemicals with large ACRs, it is likely that the mechanisms for acute and chronic toxicity differ (Welshons et al. 2003) and that the sensitivity of different taxa to acute and/or chronic toxicity varies widely. Both of these issues introduce uncertainty into the interpretation of ACRs, and probably make it inadvisable to use the FAV/FACR approach. Under such a circumstance, a prudent approach would generally be to develop a CCC directly from a sufficiently robust set of chronic data, using the procedures outlined in the *Guidelines*. If there is insufficient data from actual toxicity tests to fulfill the MDRs to develop a CCC directly from chronic toxicity data, a reasonable understanding of the toxicological MOA for the chemical may allow inferences as to what taxa (and endpoints) are most likely to be insensitive, such that measured chronic values for those taxa might not be needed. One important consideration in this process is to avoid an excessive number of taxa estimated to be insensitive, relative to those for which actual test results are available, and thus to distort the phylogenetic distribution from that implicit in the MDRs and typical of ALC.

Accordingly, the workgroup recommends that, for chemicals without complete chronic toxicity data sets fulfilling all MDRs, there be an evaluation of whether sufficient information exists to conclude that certain taxa would not be sensitive to the chemical. Given the variation in understanding and availability of data likely to exist for different CECs, it is presumed that at least initial application of this approach would have to be justified on a chemical-by-chemical basis using appropriate scientific judgment. However, lines of evidence that might be applicable to this determination include:

- an in depth understanding of the toxicological (or, in the case of drugs, therapeutic)

MOA;

- information on the basic physiology of other taxa in relation to the MOA;
- toxicity data from chronic exposures or other relevant experiments that do not meet the strict definitions of acceptable chronic data given in the *Guidelines*, but from which information on relative taxon sensitivity can be inferred; and
- information from closely related chemicals thought to have the same MOA that have more robust acute or chronic data sets.

4.3 Use of Non-Resident Species in ALC Development

Historically, EPA has not used data derived from toxicity testing with non-resident species in the actual criteria derivation process. Excluding species simply because they are not resident may be unnecessarily restrictive for the purposes of deriving national criteria, and may actually increase rather than decrease uncertainty. Because ALC are intended to protect "most of the species, most of the time" and use distributions of test data for point estimation, increasing the species representation in the toxicological database should allow better estimation of species sensitivity distributions.

The workgroup recommends that some non-resident species be considered for use in criteria derivation calculations, focusing on those species with widely used and standardized test methods and for which there is no reason to believe would misrepresent the sensitivity of comparable resident species. Furthermore, we specifically suggest accepting data for zebrafish (*Danio rerio*) and Japanese medaka (*Oryzias latipes*), to reflect international efforts toward data equivalency (Ankley and Johnson 2004). This recommendation pertains to the direct use of chronic toxicity data in the calculation of a CCC as is currently done for resident species. It is worth noting that even non-resident species that are not included in criteria calculations may still provide important information on MOA, sensitivity of endpoints, etc., as expanded on further below.

4.4 Defining Appropriate Chronic Toxicity Data

The *Guidelines* state that acceptable chronic tests for criteria derivation are full life-cycle exposures (egg/birth to egg/birth) for both vertebrates and invertebrates, as well as partial life-cycle (adult to juvenile) and early life-stage (ELS; egg to juvenile) tests for fish. For chemicals for which sexual development/maturation or reproductive effects are of most concern, the allowance in the *Guidelines* for using ELS or partial life-cycle fish tests might need reconsideration. The *Guidelines* already give priority to life-cycle tests when they are available and show greater sensitivity than other tests. However, other information indicating the importance of sexual development and reproduction (from other species, similar chemicals, knowledge of the MOA) might also establish a basis for not considering ELS data and for requiring life-cycle or partial life-cycle tests for fish.

At present, a CCC could be derived for a chemical for which chronic toxicity data for fish are limited to ELS exposures. Because of the importance of sexual maturation and reproduction for

determining the chronic toxicity of chemicals like EDCs, the workgroup recommends strengthening the *Guidelines* such that the chronic toxicity data requirements require that either:

1) Full life-cycle data be available for at least one fish species; or

2) There is a body of experimental information indicating that life processes outside the ELS or partial life-cycle exposure/observation windows would not be important to capturing the important toxicological effects of the chemical.

We note further that although this report is focused on CECs, this recommendation may be important to implement for all chemicals, not just CECs.

Regarding the latter, we recognize that there may be circumstances where the information that shows the sensitivity of different life stages comes from studies that, while scientifically valid, for some reason do not meet all the requirements of a valid life-cycle test as defined in the *Guidelines*. Alternatively, there may be data from experiments that violate other requirements of acceptable toxicity tests under the *Guidelines*, but still provide insight into sensitive exposure periods or life processes. Even though chronic values from such data may not be used directly to calculate a CCC, it seems a reasonable use of such data to evaluate the question of where in the life-cycle there are important windows of exposure and/or effect, and how that impinges on criteria derivation.

It may also be that meaningful chronic toxicity data could be developed from exposures that have a structure different from the life-cycle, partial life-cycle, and ELS protocols defined explicitly in the *Guidelines*; e.g., a short-term (21-day) reproduction assay with the fathead minnow (U.S. EPA 2001) or a multi-generational study – see example for EE2 reported in Nash et al. (2004). While defining such alternate protocols is beyond the scope of this document (see Ankley and Johnson 2004 for more detail), we recognize the potential for such a situation and leave it to appropriate implementation of the "Good Science" clause to allow for inclusion of such alternative test protocols as surrogates for chronic toxicity data, most likely in addition to, rather than instead of, data from life-cycle toxicity tests.

4.5 Selection of Effect(s) Endpoints Upon Which to Base ALC

Although chronic criteria typically are based on direct effects on reproduction, growth, and survival, there may be other endpoints indirectly related to these responses that could be useful for criteria derivation. The selection of endpoints appropriate to the derivation of ALC must be tied to the narrative intent of the overall *Guidelines*. The stated goal of ALC is to "protect aquatic organisms and their uses." While the exact meaning of "protection" is not defined, there is considerable discussion in the *Guidelines* document that makes clear that protection does not mean the prevention of any measurable biological effect in any organism. Instead, there is discussion of endpoints that are "biologically important" and prevention of "unacceptable effects"; this implies that in the context of criteria there are effects that are "biologically unimportant" and/or levels of effect that are "acceptable."

Chronic test data and other data should be examined to determine whether, for the specific chemical or MOA, endpoints beyond those traditionally used for criteria derivation may have intrinsic "biological importance" and therefore could be used as a basis for defining threshold of effect (e.g., sex ratio). Specifically, in the context of EDCs:

- Other "endocrine-sensitive endpoints" (e.g., VTG, testis-ova) should be examined to determine whether they can be relied upon as definitive indicators of other biologically important endpoints (e.g., reproduction), with the idea that they may be incorporated into calculation of the criterion. Important sources of this information would include full life-cycle tests in which these other endpoints were measured alongside traditional chronic endpoints, and may include tests with other chemicals with the same MOA (e.g., E2 for EE2).
- If endpoints, such as VTG or testis-ova, are used as direct or indirect indicators of effect, it is critically important that the baseline condition (e.g., variation during normal development) be understood sufficiently to define when changes are biologically meaningful.
- Selection of appropriate endpoints (and their associated effect thresholds) may, in some instances, transcend "biological importance" (the focus of the *Guidelines*) to reflect societal concerns (e.g., physical appearance of wild-caught fish).

4.6 Involvement of an Expert Panel

As becomes clear from the preceding issues, development of appropriate criteria for CECs may be unusually dependent on technical interpretations of a wide range of toxicological information pertinent to specific chemicals. One of the recommendations from a SETAC Pellston workshop (Mount et al. 2003), consistent with much of the above, was that expert panels be used to provide professional judgment during stages of the problem formulation and data interpretation associated with criteria development, particularly for chemicals with specific MOA. The involvement of the panel would "ensure consideration of other existing data for the chemical of concern, enable a significant degree of up-front technical input, and provide a level of peer review that should facilitate wider and more ready acceptance of the recommended criteria." The workgroup agrees with this recommendation and suggests that it be incorporated into criteria development of CECs.

To maximize effectiveness, this panel should be convened very early in the criteria development process such that it will be able to assist in problem formulation, identification of important data, and scoping of particular issues that will be important. We envision these panels as being formed around specific chemicals, or groups of chemicals with a similar MOA, in order to access the most specialized expertise available.

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WHITE PAPER

AQUATIC LIFE CRITERIA FOR CONTAMINANTS OF EMERGING CONCERN

PART II

ILLUSTRATION OF RECOMMENDATIONS USING DATA FOR 17α-ETHYNYLESTRADIOL (EE2)

Prepared by the
OW/ORD Emerging Contaminants Workgroup

June 03, 2008

NOTICE

THIS DOCUMENT IS AN INTERNAL PLANNING DOCUMENT

It has been prepared for the purpose of Research & Development Planning.
It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency guidance or policy.

DRAFT DOCUMENT

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1.0 INTRODUCTION

In Part I of this white paper, toxicological characteristics of some contaminants of emerging concern (CECs) important to the derivation of ambient water quality criteria for aquatic life (aquatic life criteria, ALC) were described, and recommendations were made to facilitate ALC derivation for these chemicals. In Part II of this white paper, toxicity data for a model CEC, 17α-ethynylestradiol (EE2), are used to further illustrate and explore those recommendations. Ethynylestradiol was chosen as a model compound for a several reasons. First, it possesses many of the toxicological characteristics described in Part I, and sufficient toxicity data exist to allow evaluation of the principles underlying the Part I recommendations. Second, toxicological effects of EE2 have been found both in the laboratory, the source of toxicological data for criteria development, and in the field, where criteria are used to enforce the regulatory authorities of the Clean Water Act. Finally, there is interest in deriving an EE2 ALC, and using EE2 as a basis for discussion should help advance that goal. While acknowledging that interest, it is important to note that the data and discussion presented are not intended to represent the formulation of an actual ALC, and potential ALC concentrations should not be inferred. The information from the ecotoxicological literature used here is for illustrative purposes and should not be considered as comprehensive, nor have all the data been fully examined for quality and applicability to ALC development.

The synthetic estrogenic steroid EE2 is the active pharmacological component of most oral contraceptives, and acts as a potent estrogen receptor agonist in vertebrates. After use and excretion of the contraceptive, domestic sewage treatment plant (STP) effluents become the primary source of EE2 entering the aquatic environment (Damstra 2002). Kolpin et al. (2002) found EE2 in 5.7% of 139 streams monitored in the U.S. While the concentrations of EE2 in Kolpin et al. (2002) have been debated (Ericson et al. 2002; Till 2003), other studies have noted concentrations ranging from 0.1 – 5.1 ng/L in surface waters (as reviewed by Campbell et al. 2006). Overall, it is somewhat uncertain at this time how high environmental concentrations of EE2 may be. Reliable analytical methods for the detection of EE2 have not been in existence very long, nor have they been widely validated in independent multi-laboratory studies. Some modeling efforts by the pharmaceutical industry indicate that based on the level of production and use of EE2 in the U.S., concentrations found in effluents should be less than 1 ng/L (Anderson, P.D. and D'Aco, V, personal communication, 2008). Complicating assessment of the possible risk of EE2 is the fact it co-occurs in STP effluents with the natural steroid hormones estradiol and estrone, though EE2 is generally found at lower concentrations. These three estrogens reportedly account for the majority of the estrogenic activity present in domestic wastewater effluents (Desbrow et al. 1998; Snyder et al. 2001), but EE2 is the most potent and resistant to degradation of the three (Nash et al. 2004; Gross-Sorokin et al. 2006). Data collected from fish and surface waters downstream of STPs over the past decade have implicated steroidal estrogens as the primary constituents in domestic effluents leading to the occurrence of intersex fish (Gross-Sorokin et al. 2006).

The remainder of this part of the white paper consists of a brief description of some relevant acute and chronic toxicity data available for EE2 (Section 2) and the evaluation of these data with respect to the recommendations made in Part I (Section 3).

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2.0 DESCRIPTION OF THE ACUTE AND CHRONIC TOXICITY DATA SUMMARIZED FOR EE2

Acute and chronic toxicity data were identified via a literature search and review of relevant articles from EPA's ECOTOX database in April 2007. This list of potentially useful articles was supplemented with a few additional reports and articles as they became published or available. Only those studies with EE2 effect data on individual aquatic organisms or their populations were retained. For this particular effort, all endpoints expressing effects of EE2 at the whole animal and cellular levels were initially considered. Because the EE2 dataset is relatively large, and because many studies report more than one endpoint of possible consideration for ALC development, the data have been broadly summarized in an appendix (Appendix A). The tables comprising Appendix A are organized by endpoint, and include separate tables for endpoints typically used to derive ALC (survival, growth and reproduction) as well as for other endpoints relevant to the estrogenic mode of action of EE2. Table A.1 contains the data available on the acute (lethal) toxicity of EE2 to aquatic animals. This table is followed by others containing the chronic (long-term) effects of EE2 on survival (Table A.2) and growth of aquatic animals (Table A.3). Tables A.4 through A.9 present data directly (fecundity, fertility) or indirectly (sex reversal, intersex, sexual behavior, vitellogenin) related to the effects of EE2 on reproduction. Finally, Table A.10 presents a summary of the significant effects of EE2 on aquatic animals based on other potentially relevant endpoints. *In vitro* effects were not considered in the data analysis.

Within each table in Appendix A, data are first separated by studies where significant effects were observed, and then by studies where significant effects were not observed (i.e., where no effect was observed at the highest concentration tested). Each table in the appendix combines data for aquatic vertebrates and invertebrates for both freshwater and saltwater species, the latter designated by asterisks. All tables are organized by increasing effect concentrations, and all chronic effect endpoints are as reported by the authors.

Many studies of the effects of EE2 on aquatic organisms did not use standard toxicity test protocols, particularly those measuring sublethal responses. This is probably due in part to these studies having been designed for purposes other than ALC development, such as exploration of toxicity mechanisms, identification of sensitivity windows, bioassay development, etc. Adequate quantification of effect concentrations is also difficult for some of these studies because of the use of widely spaced treatment concentrations and by problems with analytical detection of exposure concentrations near the threshold for reproductive effects. While the results from such studies might limit their use in ALC development according to the definitions in the *Guidelines*, they were included in this document because they may inform other aspects of criteria derivation, as explained in general terms in Part I and in detail in the sections that follow.

3.0 EE2 DATA EVALUATION AND CONSIDERATIONS FOR ALC DEVELOPMENT

This section considers the application of the data in Appendix A toward criteria derivation in the context of the several areas of concern and general recommendations identified in Part I of this white paper.

3.1 RELEVANCE OF ACUTE TOXICITY EFFECT LEVELS IN SETTING ALC FOR EDCS

One of the recommendations from Part I of this document was to determine whether the acute sensitivities of aquatic organisms to a chemical of interest are sufficient, relative to chronic sensitivity and expected exposures, to warrant derivation of a criterion maximum concentration (CMC) under the *Guidelines* procedures. This is especially important if there is not sufficient acute toxicity data to meet the minimum data requirements of the *Guidelines*, in order to avoid wasting resources on unnecessary additional testing. EE2 provides a good example of a chemical having insufficient acute toxicity data to derive a CMC according to *Guidelines* procedures, but enough data to demonstrate that deriving a CMC is not necessary.

Table 3.1 provides information on GMAVs that might be considered in CMC derivation. These values were derived from Table A.1 for any tests meeting *Guidelines* requirements, including "greater than" values indicative of the highest tested concentration eliciting less than 50% mortality. For genera without such acceptable tests, EC50/LC50s from Table A.1 for tests of 24 h duration and from Table A.2 for tests up to 30 days were also used. The EC50/LC50 values for these longer tests are designated as "greater than" values to indicate the expectation that acute EC50/LC50s would be higher. Values for medaka and zebrafish are included in accordance with the recommendation from Part I of this document that some latitude be adopted regarding species not resident to North America. Acute tests with embryos, not usually included in CMC calculations, are also included here because they suggest greater sensitivity of this life stage.

Table 3.1. Potential GMAVs for Application to EE2 CMC.

Genus	GMAV (ng/L)	Comments
Freshwater		
Rana	>760,000	14-d test
Gammarus	>840,000	10-d test
Medaka	>1,000,000	
Danio	1,700,000	
Ceriodaphnia	1,800,000	
Hydra	3,800,000	
Sida	>4,100,000	24-h test

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Genus	GMAV (ng/L)	Comments
Daphnia	>5,000,000	
Chironomus	9,100,000	24-h test
Saltwater		
Lytechinus	30,000	Embryo
Strongylocentrotus	30,000	Embryo
Acartia	88,000	Embryo
Tisbe	>100,000	21-d test
Acartia	1,100,000	
Neomysis	1,200,000	

The data summarized in Table 3.1 show several deficiencies in meeting the minimum data requirements for deriving a CMC under the Guidelines. For freshwater application, only four genera, rather than the minimum of eight, meet the acute test requirements, even if the prohibition for non-resident species is ignored. If the shorter and longer tests are included, the requirement of at least eight genera is met, but the requirement for a salmonid fish is not. Even if this requirement is also ignored, two of the lowest four genera are "greater than" values, whereas CMC calculations can only be made if the four most sensitive genera have definite values ("greater than" values are permitted only for more tolerant genera.) For saltwater, there are even greater deficiencies in meeting the minimum data requirements.

Although these data are insufficient for deriving CMCs, they do provide ample evidence that a CMC is not needed and that it is unnecessary to conduct further tests to meet the minimum data requirements. For freshwater, there is still a rather broad taxonomic representation, including three vertebrates from two different classes, four crustaceans from two orders, and a third phylum. The acute LC50s/EC50s are consistently near and above 1 mg/L, several orders of magnitude above both the most sensitive chronic endpoints (Tables A.4 – A.9) and the highest environmental concentrations that organisms might be exposed to. The saltwater data do show greater sensitivity for the embryonic stages of some genera, but whether this reflects a lifestage or taxa sensitivity issue, these LC50s/EC50s are still four orders of magnitude above the most sensitive chronic endpoints and environmentally-relevant exposures.

3.2 USE OF NON-RESIDENT SPECIES IN ALC DEVELOPMENT

Under the *Guidelines*, toxicity values from aquatic species not resident to the contiguous 48 United States, Alaska, or Canada are excluded from ALC derivation. One of the recommendations in Part I of this white paper is that this prohibition be relaxed and that data for non-resident species be allowed where deemed suitable, especially for species such as medaka and zebrafish which have become standard test organisms commonly used worldwide. Any tested species, whether resident or not, serves as a surrogate for estimating a sensitivity

distribution relevant to assessing risks in a variety of aquatic communities with a multitude of untested species. Therefore, the issue here is whether a non-resident species can serve as a reasonable surrogate for assessing the sensitivity of untested resident species. The use of such species would still be contraindicated if there is reason to believe they are significantly more or less sensitive than resident species.

The data in Appendix A support the use of medaka and zebrafish data in criteria calculations. Although there are no resident fish species with which to compare the acute sensitivities of medaka and zebrafish (see Table 3.1 and Table A.1), their lack of acute sensitivity is consistent with that of resident amphibians and invertebrates in the available data. The sensitivities of these fish species for long-term survival (Table A.2), growth (Table A.3), and reproduction (Table A.4) are interspersed with those of resident fish species, so there is no indication of either substantially higher tolerance or sensitivity to contraindicate their use. This is also generally true of the other endpoints summarized in Appendix A. The similarity among fish species of different geographic origins is not surprising, since the MOA of EE2 involves receptors and pathways that are highly conserved among vertebrates. If similar trends are seen in the data once they are thoroughly examined for quality and applicability to ALC development, data from these non-resident species should be included in criteria development.

The data in Appendix A also underscore pragmatic advantages of including non-resident species in criteria development. Medaka and zebrafish provided a large fraction of the available data regarding EE2 effects on fish. Removing them from the dataset simply because they are not resident would limit information on the distribution of species sensitivity and may actually increase rather than decrease uncertainty regarding resident species. Another use of data from non-resident species could be to assist in extrapolations of information across species, chemicals, and endpoints. For example, life-cycle tests with medaka could be used to evaluate whether early life-stage or partial life-cycle tests with resident species should or should not be accepted in criteria calculations for specific classes of chemicals with a defined MOA. The relationship of reproductive effects in non-resident fish (Table A.4) to other endpoints (Tables A.5-A.9) could also be used to determine how to apply information on these other endpoints for resident species lacking direct toxicological information on reproduction.

3.3 MINIMUM DATA REQUIREMENTS REGARDING TAXONOMIC COVERAGE

As discussed in section 3.1, deriving a CMC for EE2 is not useful because acutely-toxic concentrations are so much higher than both chronic effects concentrations and expected environmental concentrations. In addition, developing a CMC would require additional acute toxicity tests to meet the minimum data requirements (MDRs) specified in the *Guidelines*. Without a CMC, the criterion continuous concentration (CCC) must be calculated directly from the available data, rather than through extrapolation using an acute to chronic ratio (ACR); this is probably not advisable anyway for such large ACRs. Since the ACR method is moot, the *Guidelines* calculation procedures for the CCC require that there be sufficient chronic toxicity tests to satisfy the MDRs for estimating the fifth percentile of the chronic database. For

freshwater criteria, these MDRs include a species from: the family Salmonidae; a species from a second family in the class Osteichthyes; a species from a third family in the phylum Chordata; a planktonic species from the Class Crustacea; a benthic species from the Class Crustacean; a species from the Class Insecta; a species from a phylum other than Chordata or Arthropoda; and a species from an order of insects or a phylum not otherwise represented.

Few existing ALC have chronic data that meet the MDRs, and this will likely be true of CECs as well. Significant expense would be incurred conducting new chronic tests to satisfy all the requirements. As recommended in Part I of this white paper, because only the four most sensitive genus mean chronic values (GMCVs) are used in the criteria calculations, chronic testing requirements for a taxon needed to meet an MDR should be waived if there is sufficient information to conclude that this taxon is more tolerant than the four most sensitive genera. A value (or values) for this taxon would still be included in the data set, but its GMCV would simply be specified to be greater than the fourth lowest GMCV.

Table 3.2 lists chronic values for the toxicity of EE2 to various freshwater genera to illustrate data that might be included in freshwater criteria calculations. These chronic values were obtained from Tables A.2-A.4, using *Guidelines* data selection procedures where possible, but also included some additional data to support discussion of how certain data deficiencies might be addressed. For invertebrates, the *Guidelines* require life-cycle tests that include reproductive endpoints, but if that type of test was not available, then other tests are reported here, with their limitations noted. For fish, the *Guidelines* preference order of life-cycle, partial life-cycle, and early life stage (ELS) was followed, but other tests were also reported as needed for illustrative purposes, with their limitations also noted. For all genera, the most sensitive endpoint among chronic survival, growth, and reproduction was selected, which was from the reproduction data of Table A.4, except for *Chironomus* (for which development from egg to pre-emergence was tested and the effects concentration was from Table A.3). Each chronic value (CV) was calculated as the geometric mean of the reported no observed and lowest observed effect concentrations (NOEC and LOEC) for an adverse effect. When the LOEC was the lowest exposure concentration, a "less-than" concentration is reported for the CV and, when the NOEC was the higher exposure concentration for insensitive species, a "greater-than" concentration is reported. As explained in Sections 1 and 2, these data are still under review and subject to modification. The specific values here should not be misconstrued as final, but rather as examples to illustrate trends and indicate needs that support the recommendations being addressed here.

Table 3.2. Potential Chronic Values for Application to EE2 CCC.

Genus	CV(s) (ng/L)	Notes
Danio	0.6, 1.5, <1.1	Life-cycle tests; for 1.5 ng/L CV, there was a 9-fold difference between LOEC and NOEC and the LOEC was a 100% effect
Pimephales	<0.32, 1.5	Life-cycle tests; for <0.32 ng/L CV, LOEC showed reduced fertilization but increased egg production so total reproduction not adversely affected; for 1.5 CV, 4-fold difference between NOEC and LOEC
Oryzias	3.2	F_0 from 1 d through spawning; 10-fold difference between NOEC and LOEC
Oncorhynchus	<16	Adult exposure only; fertilization success only endpoint examined
Potamopyrgus	50	Adult exposure only; embryo production over 9 wk test
Gammarus	>7,600	Population size over 100 d test; increased population size at 760 and 7,600 ng/L
Daphnia	45,000	5-fold difference between NOEC and LOEC
Tisbe	>100,000	Saltwater copepod included to further indicate arthropod insensitivity
Chironomus	320,000	Larval growth and molting schedule only; did not include emergence and reproduction
Brachionus	800,000	Intrinsic rate of population increase over 72 hr test

The data in Table 3.2 indicate high sensitivity of vertebrates to EE2. Significant reproductive effects in the life-cycle tests for zebrafish (*Danio rerio*) and fathead minnow (*Pimephales promelas*) occur at concentrations near and perhaps below 1 ng/L. Although the chronic test for medaka (*Oryzias latipes*) did not cover the entire life cycle, it included life stages likely important for reproduction and indicated a sensitivity similar to zebrafish and fathead minnow. For rainbow trout (*Oncorhynchus mykiss*), a more limited exposure addressing only effects on fertilization suggests that reproductive effects on this species should also be present in the low ng/L range. However, the absence of a definite toxicity value for rainbow trout will be an important impediment to criteria calculations, both for leaving an MDR unsatisfied and for being one of the four most sensitive genera in this set. Actual criteria development will require a decision whether to (a) require more information for this species, (b) use other information to help estimate rainbow trout sensitivity or (c) justify setting the MDR aside (see Section 3.5).

The invertebrate data in Table 3.2 indicate lower sensitivity, especially for arthropods (*Gammarus, Daphnia, Tisbe*, *Chironomus*) and rotifers (*Brachionus*). Some data, like the *Chironomus* test, fail to satisfy the *Guidelines* requirement for a life-cycle test and the copepod *Tisbe* is a saltwater species included here only to reinforce conclusions about arthropod sensitivity. Also, the tests for *Gammarus* and *Brachionus* are not standard life-cycle tests, but could be considered to satisfy *Guidelines* requirements because exposures span a life cycle and

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include reproductive effects. The snail (*Potamopyrgus*) toxicity test showed moderate sensitivity, although still about an order of magnitude less than the fish, and also does not involve a full life-cycle test.

These data demonstrate the potential for a situation in which the GMCVs for taxa reasonably expected to be insensitive do not need to be quantified. For example, although the *Chironomus* test was not a full life-cycle test and thus could not fully define the GMCV under *Guidelines* requirements, it indicates such a degree of insensitivity for growth and development, such that it can be reasonably presumed that a full life-cycle test would still show much less sensitivity than the vertebrates, especially because other arthropods are observed to be similarly insensitive. Likewise, the snail test, although not for a full life-cycle, involved the effects of long exposures on reproduction, and can be argued to be sufficiently less sensitive than fish reproduction so that it would not reasonably be expected to be among the four most sensitive genera if a life cycle test was conducted. These inclusions, along with the data for *Daphnia*, *Gammarus*, and *Brachionus*, satisfy the *Guidelines* MDRs for invertebrates, and would allow an ALC to be calculated from the four sensitive vertebrate genera, provided the value for the rainbow trout was resolved.

Assessing that taxa are likely to be insensitive could involve other lines of evidence, especially for CECs with more limited chronic toxicity data than EE2. Tests involving endpoints such as those in Tables A.5-A.10 could be used to establish that certain taxa are sufficiently less sensitive than others to preclude the need for tests on their chronic survival, growth, and reproduction (Tables A.2-A.4), the endpoints typically used in ALC development. Information from other chemicals might also be used, such as using the insensitivity of arthropods to EE2 to preclude testing this taxonomic class with chemicals with the same MOA. Such a strategy could be used to help the evaluation of EE2, particularly regarding the snail sensitivity. For example, the sensitivity of this or similar species relative to that of vertebrates for other chemicals could be used to strenghten a conclusion that they are less sensitive to EE2 than are fish.

3.4 DEFINING APPROPRIATE CHRONIC TOXICITY DATA

As discussed in Part I of this white paper, characteristics of some CECs require that careful consideration be given to the selection of chronic toxicity data appropriate for ALC development. Specifically, the use of data from early-life stage (ELS) or partial-life cycle (PLC) exposures as estimates of life-cycle chronic effect thresholds is inadvisable for chemicals whose MOA would result in biological effects for which critical periods of induction and/or expression would lie outside the exposure/observation window provided by the test procedure.

An examination of data specifically for EE2 provides evidence to support emphasis on full life-cycle exposures for determining the chronic toxicity of EE2. Länge et al. (2001) conducted a full life-cycle chronic exposure with fathead minnows which were exposed from fertilized eggs (F_0) through maturation, spawning, and early-life stage development of the F_1 generation. Nominal exposure concentrations of EE2 were 0.2, 1, 4, 16, and 64 ng/L (for convenience, nominal concentrations are used in this discussion as the important point is relative endpoint sensitivity

rather than absolute concentrations inducing effects). As part of this exposure, measurements of growth (as length) and survival were made at 28 days post hatch (dph) which would correspond to the end of a standard ELS exposure with fathead minnows. At 28 dph, there were no effects on survival. The length endpoint showed a 16% reduction at 64 ng/L, a smaller but significant reduction of 6% at 16 ng/L, and no effect at 4 ng/L. Accordingly, the NOEC and LOEC for an ELS test with EE2 would have been 4 and 16 ng/L, respectively, and an EC20 based on length would be >64 ng/L. However, as exposure continued throughout the life cycle, pronounced effects were observed for other endpoints at lower exposures. There was no reproduction at all in fish exposed to 4 ng/L, and a trend, though not significant, toward lower reproduction at 0.2 and 1 ng/L. Other significant effects observed included a 16% reduction in weight of adult female fish at 1 ng/L after 301 d exposure, and 5 to 10 percent reductions in weight of F_1 offspring at 28 dph, though the authors questioned the biological significance of the F_1 growth effects. Regardless, the clear indication is that life-cycle exposure showed substantially greater sensitivity to EE2 than was evidenced from ELS endpoints alone. This was much larger than the factor of 2 difference generally found for other chemicals by McKim et al. (1978).

A similar conclusion can be drawn from the study of Parrott and Blunt (2005). This involved exposure from fertilized egg through reproduction, including measures of fertilization success (but not ELS development) in the F_1 generation. Exposure was to nominal concentrations of 0.32, 0.96, 3.2, 9.6, and 32 ng/L EE2. Measurements of survival and growth at 30 dph showed no effects (NOEC $\geq$ 32 ng/L). However, continuation of exposure through adulthood showed no reproduction in the 3.2, 9.6 and 32 ng EE2/L treatments, and all fish in these treatments were phenotypic females. There was also suggestion of effects on fertilization success at 0.32 and 0.96 ng/L, although interpretation of these effects is complicated by an increase in number of eggs produced in these same treatments, such that the total number of fertilized eggs was not as dramatically affected. Regardless, the message relative to definition of chronic sensitivity is the same in that effects were apparent after life-cycle exposure at concentrations well below those that would be expected to show effects in an ELS test.

Additional comparisons can be extracted from the work of Wenzel et al. (2001), who conducted a multi-generational study of zebrafish exposed to EE2 concentrations from 0.05 to 10 ng EE2/L. Observations of survival and length of exposed fish showed no effects at 21 and 42 dph (NOEC $\geq$10 ng/L). However, with continued exposure, a variety of effects were observed around an EE2 test concentration of 1 ng/L, including effects on adult length, time to spawning, egg production and fertilization. As for the fathead minnow studies, survival and growth measured during the period comparable to an ELS study were far less sensitive to EE2 exposure than were endpoints measured in full life-cycle studies (Tables A.2, A.3, A.4).

The reason for these differences between ELS and full life-cycle tests is obvious when one considers the MOA for EE2, which interferes with sexual differentiation, development, maturation, and spawning. Because the endpoints measured in ELS tests are limited to survival and growth, and because the effects of EE2 on sexual differentiation are not apparent (at least not at a gross morphological level) in the tested species by 28-30 dph, the ELS test is comparatively insensitive to toxicity mediated through an estrogen receptor signaling pathway. It is interesting

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to note that even though a standard ELS test is relatively insensitive to detecting the effects of EE2 exposure, other work has shown that key windows of exposure do in fact occur during the ELS exposure window. Van Aerle et al (2002) demonstrated that larval fathead minnows exposed to EE2 only during brief windows during early development (e.g., 10-15 dph) showed altered sexual development of male fish at 100 dph, including the development of an ovarian-like cavity and changes in the distribution of testicular cell types (Table A.6). The issue for interpreting chronic toxicity data is that, even though effects may be induced during ELS exposure, they are not expressed unless exposed fish are observed later in sexual development.

This latter observation also has implications for the suitability of PLC tests for detecting the effects of EE2 or other chemicals acting through a similar pathway. As discussed in the *Guidelines*, PLC tests are acceptable chronic tests for fish species that require more than one year to reach sexual maturity, such as the common species of trout. PLC tests are to begin exposure "with immature juveniles at least 2 months prior to active gonad development, continue through maturation and reproduction, and end not less than 24 days (90 days for salmonids) after the hatching of the next generation." If salmonids (or other species for which PLC tests might be conducted) were to express effects from larval exposure to EE2 as observed by Van Aerle et al. (2002) for fathead minnows, one would expect that a PLC exposure would not be as sensitive as a full life-cycle exposure. That is, even though a PLC test includes the observation periods shown to be sensitive in full life-cycle exposures, it might not include the exposure windows important to inducing chronic effects on sexual differentiation and development.

While the rationale for emphasizing full life-cycle chronic tests has clear grounding in the MOA for EE2, it has practical implications in terms of the fish species likely to be tested. Most species for which life-cycle chronic tests are most commonly conducted (primarily fathead minnow, zebrafish, medaka, flagfish, and sheepshead minnow), are small fish that develop rapidly and are continuous spawners (as opposed to annual spawners like rainbow trout or bluegill sunfish). Whether or not these life history traits influence sensitivity to EE2 is unknown, but because of the investment necessary to conduct true life-cycle exposures with annually spawning fish that take much longer to develop, it may be unlikely that comparative data will be developed. Better understanding these implications is a worthy subject for future research.

Finally, there are some scattered indications in the literature for trans-generational effects of EE2 exposure. As mentioned above, Länge et al. (2001) found small effects on growth in the F_1 generation that were not observed after comparable exposure of the F_0. Wenzel et al. (2002) also report some suggestions of growth inhibition in subsequent generations at exposure below those causing such effects in the first exposed generation (Table A.3). The mechanisms by which such effects might occur are not clear, nor are their implications (in fact, Länge et al. actively dismiss them as being biologically unimportant). At this point, it does not seem that the evidence for trans-generational effects is sufficient for requiring their inclusion in the definition of an acceptable chronic test, but the potential for the existence and importance of trans-generational effects should be re-evaluated in the future as additional data become available.

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3.5 SELECTION OF EFFECT(S) ENDPOINTS UPON WHICH TO BASE ALC

Aquatic studies with EE2, particularly those using fish, have measured a variety of endpoints not traditionally used for criteria derivation, including reproductive behavior, abnormal sex ratios, changes in secondary sexual characteristics, altered histopathology (typically gonadal), changes in steroid hormones, and modifications in the expression (or activity) of a variety of proteins/enzymes. Many of these endpoints were evaluated because they are known (or hypothesized) to be responsive to estrogenic MOA, and not because the intended result was the quantitative assessment of risk. Among the challenges in using data from these types of mechanism-based endpoints is that such measurements are seldom standardized or straightforward in their interpretation. For example, alterations in behavior are difficult to objectively quantify, it is challenging to accurately measure steroid hormone concentrations in small fish, and the capability of measuring gene expression or enzyme activity can be quite lab/method-specific. A second source of uncertainty in using most of the mechanism-specific endpoints evaluated in EE2 studies is a lack of knowledge concerning the functional relationship between changes in endpoints and responses of primary concern for risk assessment, such as survival, growth and reproduction. Even in considering these challenges related to measurement and interpretation, however, there are a handful of mechanistic endpoints/responses that exhibit utility for supporting ALC derivation for EE2 (or other xenobiotic compounds with estrogenic activity). Three of these are discussed in greater detail below.

A frequently measured mechanism-specific endpoint in fish exposed to EE2, is induction of vitellogenin mRNA (*vtg*) or expression of circulating vitellogenin protein (VTG) in males (Table A.9). The most attractive attribute of this endpoint is its specificity for an estrogenic MOA, since there are no other chemically linked biological phenomena known to consistently activate the vitellogenin gene or elevate vitellogenin protein in male fish. Further, since the vitellogenin gene is quiescent in male fish, which implies a zero baseline of vitellogenin, the response is unambiguous with regard to exposure. Additionally, this exposure mediated induction of *vtg* is sensitive to low levels of exogenous estrogen. Because vitellogenin protein has been frequently evaluated in fish studies, accurate methods of measurement (including several commercial kits) are available for many fish species, including the small fish models for which much of the EE2 chronic toxicity data exist. Given these attributes, male VTG has and should continue to be a very useful endpoint for monitoring the occurrence of estrogenic chemicals (including EE2) in the environment. A major drawback to using male-specific circulating protein to assess exposure and risk of EE2 (or other estrogens), including the derivation of ALC, is the lack of an established functional linkage between expression of the protein and adverse endpoints related to early development or reproduction (Wheeler et al. 2005). This is in large part due to the fact that VTG plays no physiological role in male reproductive processes. As such, any associations that might exist between VTG induction in males and reproductive success is likely more correlative than causal.

Despite the fact that the appearance of VTG in males appears not to be a robust predictor of adverse effects on reproduction, the response could nonetheless play an important role in reducing the uncertainty of ALC for EE2, or the development of ALC for other chemicals which

might be estrogenic. From Table 3.2 above, it is apparent that data from life-cycle tests with fish would be appropriate (and critical) to setting the final ALC for EE2 and, by extension, other estrogens. Hence, knowledge that a less well-studied chemical than EE2 induces VTG in males could be used to help identify those instances when one (or more) life-cycle fish assay(s) would be recommended for generating robust data for ALC derivation. Another possible use of protein data, that could have more direct applicability to developing an ALC for EE2, involves use of the endpoint as a basis for evaluating relative species sensitivity. Specifically, reproductive data suitable for an EE2 ALC are largely from three species: fathead minnow, medaka and zebrafish (Table 3.2); however, there are studies with numerous species that have evaluated the ability of EE2 to induce vitellogenin mRNA and protein in males. Provided that a common dose metric could be established across these studies, a dataset could be developed to provide an indication of the relative sensitivity distribution of fish species to EE2, in addition to other estrogens. This would enable a direct comparison of values along the continuum of estrogen sensitivity for those fish species wherein chronic data exist (based on VTG induction) and, as such, could provide a quantitative indication of uncertainty for a proposed EE2 criterion.

There are two mechanism-specific endpoints that have been measured in a number of EE2 studies that might, with additional research and analysis, have a direct bearing on criteria derivation: alterations in sex ratio (i.e., generation of genotypic males with a female phenotype) and the occurrence of intersex/testis-ova (Tables A.5, A.6). As opposed to VTG induction in males, the functional linkage between skewed sex ratios or abnormal gonad development and reproductive success in fish, at both the individual and population levels, is readily apparent. Specific endpoints, however, can be difficult to measure. For example, detailed histological analyses are needed to identify and, especially, quantify testis-ova. To detect an alteration in sex ratio, a genotypic marker of gender (available in medaka but not fathead minnow or zebrafish) or a relatively large representative sample is required to reliably detect chemically-induced changes within a proportion of males and females in a population. Probably more difficult than measurement of the endpoints is definition of the quantitative linkage between changes in sex ratio or occurrence of testis-ova and effects on reproductive success for individuals and populations. For example, unless one assumes that any deviation in sex ratio from the norm (e.g., 1:1) is adverse, it is necessary to know (in the case of estrogenic effects) the magnitude of shift in respective gender numbers that is likely to result in cases where fewer young are produced. Similarly, it is probable that some degree of testis-ova would not be considered adverse in terms of reducing reproductive success, especially considering that the condition can exist at some degree, even in control animals (Grim et al. 2007). It is certain that at some level of manifestation, the condition will impair gonad function sufficiently such that acceptable levels of normal sperm cannot be produced. The frequency of this phenomenon, however, is currently unknown for any fish species. Definition of this relationship would support use of testis-ova occurrence in fish not only for prospective assessments (like criterion derivation), but in environmental monitoring studies focused on chemicals with an estrogenic MOA.

At present, uncertainties regarding measurement and interpretation hamper use of data from any of the mechanism-specific endpoints mentioned above as a basis for derivation of an ALC for EE2. Eith appropriate research, however, induction of vitellogenin in males, changes in sex

ratios and occurrence of testis-ova, all have the potential to contribute insights to different facets of quantitative risk assessment for estrogenic chemicals, including derivation of ALC. There is one noteworthy additional observation relative to use of non-traditional endpoints for an EE2 ALC. Several fish life-cycle studies using EE2 have been conducted in which typical measures of reproductive success (e.g., fecundity, fertility) have been made in conjunction with induction of VTG, sex ratio and/or testis-ova data (e.g., Länge et al 2001; Wenzel et al. 2001; Nash et al. 2004; Parrott and Blunt 2005). Although experimental design variables make some of the endpoint sensitivity comparisons challenging, it does not appear that there are substantial differences in EE2 test concentrations that produce adverse effects on egg production/fertility, versus those that alter the mechanism-specific endpoints. Hence from a pragmatic perspective, at least for the near-term, it seems reasonable to base an EE2 ALC on traditional measures of long-term reproductive success in fish.

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APPENDIX A

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Table A.1. Effects of EE2 on Aquatic Animals (Short-term survival).

Species	Life stage	Method	Duration	EC50 or LC50 (ng/L)	Reference	Remarks
Traditional Acute (1-7 day timeframe)						
*Sea urchin, *Strongylocentrotus purpuratus*	embryo	S,U	96 h	30,000	Roepke 2005	EC50 - abnormal development
*Sea urchin, *Lytechinus anamesus*	embryo	S,U	96 h	30,000	Roepke 2005	EC50 - abnormal development
*Copepod, *Acartia tonsa*	egg	R,U	5 d	88,000	Andersen et al. 2001	EC50-Inhibition of naupliar development
Medaka, *Oryzias latipes*	adult	-	96 h	>1,000,000	Thompson 2000	
*Copepod, *Acartia tonsa*	10-12 d adult	S,U	48 h	1,100,000	Andersen et al. 2001	
*Opossum shrimp, *Neomysis integer*	Juv, 2-4 mm	R, U	96 h	1,200,000	Verslycke et al. 2004	
Zebrafish, *Danio rerio*	adult	-	96 h	1,700,000	Wenzel et al. 2001	
Cladoceran, *Ceriodaphnia reticulata*		S,U	24 h	1,800,000	Jaser et al. 2003	EC50 mobility
Cnidarian, *Hydra vulgaris*	Adult male	R, U	96 h	3,800,000	Pascoe et al. 2002	
Cladoceran, *Sida crystallina*		S,U	24 h	>4,100,000	Jaser et al. 2003	EC50 mobility
Cladoceran, *Daphnia magna*	<24 h	S,U	48 h	>5,000,000	Goto and Hiromi 2003	
Midge, *Chironomus riparius*	4th instar	S,M	24 h	9,100,000	Lee and Choi 2006	

*Indicates saltwater species.

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Table A.2. Effects of EE2 on Aquatic Animals (Long-term survival).

Species	Life Stage	Method	Duration	NOEC-survival (ng/L)	LOEC - survival (ng/L)	Reference	Remarks
Significant Effect Observed							
Zebrafish, *Danio rerio*	1 d old	R,U	38 d	10	100	Orn et al 2006	100% mortality at LOEC
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	10	100	Hill and Janz 2003	90% mortality at LOEC (45% control mortality); excess solvent
Medaka, *Oryzias latipes*	1 d	R,M	LC: 85 to 110 dph	29	290	Metcalfe et al. 2001	83% mortality at LOEC
*Sheepshead minnow, *Cyprinodon variegatus*	juv	F,M	PLC:59-7 dph F1	120	330	Zillioux et al. 2001	50% mortality at LOEC (42 days)
Medaka, *Oryzias latipes*	6 mo.	F,M	21 d	260	490	Seki et al. 2002	42% mortality at LOEC (4 of 5 dead males)
Rainbow trout, *Oncorhynchus mykiss*	1+ year	F,M	62 d pre-spawning	130	750	Schultz et al. 2003	100% mortality at LOEC (57 days)
Medaka, *Oryzias latipes*	4 mo.	R,U	14 d	500	2,000	Thompson 2000; Tilton et al. 2005	Significant mortality at LOEC
Zebrafish, *Danio rerio*	fert. eggs	R,U	5 wk	-	5,000	Ortiz-Zarragoitia et al. 2006	50% mortalty of exposed animals
*Copepod, *Tisbe battagliai*	<24 h	R,U	10 d	-	>100,000	Hutchinson et al. 1999	Value is an LC50
Wood frog, *Rana sylvatica*	Gosner 26	R,U	14 d	-	560,000	Hogan et al. 2006	Value is an LC50
Amphipod, *Gammarus pulex*	3-5 mm	R,M	10 d	-	840,000	Watts et al. 2001	Value is an LC50
Leopard frog, *Rana pipiens*	Gosner 26	R,U	14 d	-	890,000	Hogan et al. 2006	Value is an LC50
Leopard frog, *Rana pipiens*	Gosner 36	R,U	14 d	-	1,200,000	Hogan et al. 2006	Value is an LC50
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)							
*Sand goby, *Pomatoschistus minutus*	juv	F,U	7 mo	6	-	Robinson et al. 2003	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	125 d	10	-	Parrot et al. 2003	
Fathead minnow, *Pimephales promelas*	juvenile	F,M	21 d	20	-	Panter et al. 2002	Conc. only 40% of nominal

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Species	Life Stage	Method	Duration	NOEC-survival (ng/L)	LOEC - survival (ng/L)	Reference	Remarks
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	25	-	Zha et al. 2007	10% mortality
Zebrafish, *Danio rerio*	fert. eggs	F,U	3 mo	25	-	Van den Belt et al. 2003	40% mortality after 5 mo. recovery
Fathead minnow, *Pimephales promelas*	mature male	F,U	35 d	50	-	Schmid et al. 2002	
Snail, *Potamopyrgus antipodarum*	adult	R,U	9 wk	100	-	Jobling et al. 2004	
Medaka, *Oryzias latipes*	1 d	R,U	2 mo	100	-	Scholz and Gutzeit 2000	8% mortality
Zebrafish, *Danio rerio*	4 wk	R,U	33 d	100	-	Versonnen and Janssen 2004	6.6% mortality; excessive carrier solvent
Guppy, *Poecilia reticulate* (male)	< 7 d	F,M	108 d	110	-	Nielsen and Baatrup 2006	
Sturgeon, *Acipenser fulvescens*	1 yr	F,M	25 d	120	-	Palace et al. 2001	
Rainbow trout male, *Oncorhynchus mykiss*		F,M	3 wk	130	-	Hook et al. 2007	
African clawed frog, *Xenopus laevis*	adult	R,U	4 wk	2,960	-	Urbatzka et al. 2007	
Wood frog, *Rana sylvatica*	Gosner stage 25	R,M	76 d	4,100	-	Mackenzie et al. 2003	
Amphipod *Gammarus pulex*	mixed age	F,M	100 d	7,600	-	Watts et al. 2002	
Amphipod adult, *Hyalella azteca*	pre-copulatory	R,M	10 wk - 2 x gen	10,000	-	Vandenbergh et al. 2003	
*Copepod, *Tisbe battagliai*	<24 hr	R,U	21 d	100,000	-	Hutchinson et al. 1999	
*Copepod, *Tisbe battagliai*	<24 hr	R,U	21 d	100,000	-	Pounds et al. 2002	
Cladoceran, *Sida crystallina*		R,U	34 d	500,000	-	Jaser et al. 2003	
Cladoceran, *Daphnia magna*		R,U	25 d	500,000	-	Goto and Hiromi 2003	

*Indicates saltwater species.

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Table A.3. Effects of EE2 on Aquatic Animals (Growth).

Species Significant Effects Observed	Life Stage	Method	Duration	NOEC-growth (ng/L)	LOEC-growth (ng/L)	Reference	Remarks
Zebrafish , *Danio rerio*	fert egg	F,M	LC – F1	0.10	0.3	Wenzel et al. 2001	7% reduction at LOEC (75 dph)
Zebrafish , *Danio rerio*	fert egg	F,M	PLC	0.30	1.1	Wenzel et al. 2001	2% reduction at LOEC (78 dph)
Zebrafish, *Danio rerio*	20 dph	R,M	40 d	0.60	1.5	Orn et al. 2003	**Increased** juvenile wet weight
Fathead minnow, *Pimephales promelas*	<24 hr	F,M	LC	0.76	2.8	Länge et al. 2001	
Zebrafish , *Danio rerio*	fert egg	F,U	3 mo	1	10	Van den Belt et al. 2003	
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	1	10	Lin and Janz 2006	
Fathead minnow, *Pimephales promelas*	embryo	F,M	114 d	-	12	Bogers et al. 2006b	
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 days	5	25	Zha et al. 2007	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	60 dph	10	32	Parrot and Wood 2002	
Zebrafish , *Danio rerio*	4 wk	R,U	33 d	10	100	Versonnen and Janssen 2004	Excessive carrier solvent
Guppy, *Poecilia reticulata*	<7d	F,M	108 d	44	112	Nielsen and Baatrup 2006	**Increased** adult wet weight.
Medaka, *Oryzias latipes*	1 day old	R,M	LC	29	290	Metcalfe et al. 2001	
Midge, *Chironomus riparius*	4th instar	S,U	48 hr	50	500	Lee et al. 2006	I**ncreased** larval dry weight
Midge, *Chironomus riparius*	1st instar	R,M	egg - pupa	100,000	1,000,000	Watts et al. 2003	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)							
Zebrafish, *Danio rerio*	fert egg	F,M	2xGen	4.5	-	Nash et al. 2004	
*Three-spined stickleback, *Gasterosteus aculeatus*	fry	R,U	14 days	7.3	-	Hahlbeck et al. 2004b	

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Species	Life Stage	Method	Duration	NOEC-growth (ng/L)	LOEC-growth (ng/L)	Reference	Remarks
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	60 dph	10	-	Parrot et al. 2003	
Fathead minnow, *Pimephales promelas*	juv	F,M	21 days	20	-	Panter et al. 2002	
Prosobranch mollusc, *Potamopyrgus antipodarum*	adult	R,U	9 wk	100	-	Jobling et al. 2004	
*Sheepshead minnow , *Cyprinodon variegatus*	juv	F,M	PLC	330	-	Zillioux et al. 2001	
Wood frog , *Rana sylvatica*	Gosner stage 25	R,M	76 d	4,100	-	Mackenzie et al. 2003	

*Indicates saltwater species.

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Table A.4. Chronic Reproductive Effects of EE2 on Aquatic Animals (Fecundity, Fertility, and Population Growth).

Species	Life Stage	Method	Duration	Endpoint	NOEC (ng/L)	LOEC (ng/L)	Reference	Remarks
Significant Effects Observed								
Fathead minnow, *Pimephales promelas*	40-60 h	F,M	LC	Percent fertilized of eggs laid	-	0.32	Parrott and Blunt 2005	
Zebrafish, *Danio rerio*	fert egg	F,M	LC	Number of fertilized eggs per female	0.30	1.1	Wenzel et al. 2001	
Fathead minnow, *Pimephales promelas*	<24 hr	F,M	LC	Mean no. eggs laid per breeding day	0.76	2.8	Länge et al. 2001	
Zebrafish, *Danio rerio*	fert egg	F,M	118 d	No. eggs spawned and prop fertilized	-	3	Fenske et al. 2005	
Fathead minnows, *Pimephales promelas*	-	Field	3 yrs	Population crash	-	3.2 – 8.9	Kidd et al. 2007	
Green frog, *Rana clamitans*	fert egg	Field	2 yr	Hatching success	-	3.2 – 8.9	Park and Kidd 2005	
Zebrafish, *Danio rerio*	fert egg	F,M	2 x gen	Proportion of non-viable eggs	0.50	4.5	Nash et al. 2004	Complete Rep. failure at LOEC
*Sand goby, *Pomatoschistus minutus*	juv	F,U	7 months	Fertile eggs and hatching success	-	6	Robinson et al. 2003	
Fathead minnow, *Pimephales promelas*	6-11 mo.	F,M	3 wk	Fert rate and no. eggs spawned	0.75	7.5	Pawlowski et al. 2004	**Increased** No. eggs spawned up to 0.75 ng/L
Zebrafish, *Danio rerio*	2 dph	R,U	60 d	% viable eggs, % hatch, % swim-up	1	10	Hill and Janz 2003	Excessive carrier solvent
Medaka, *Oryzias latipes*	1 d	R,U	2 mo	Female egg production	1	10	Scholz and Gutzeit 2000	No effect on male fert at 10 ng/L
Zebrafish, *Danio rerio*	fert egg	F,U	3 mo	No. spawning females & egg prod	1	10	Van den Belt et al. 2003	
Zebrafish, *Danio rerio*	8 mo	R,U	14 d	Absence of intact eggs in ovaries	1	10	Versonnen and Janssen 2004	
Rainbow trout, *Oncorhynchus mykiss*	1+ year	F,M	PLC	Fertilization success	-	16	Schultz et al. 2003	EC50; same response@131 ng/L
Snail, *Potamopyrgus antipodarum*	adult	R,U	9 wk	Embryo production	25	100	Jobling et al. 2004	EE2 at 25 ng/L stimulatory
*Sheepshead minnow, *Cyprinodon variegatus*	juv	F,M	PLC	Hatching success	18	120	Zillioux et al. 2001	
Medaka, *Oryzias latipes*	6 mo.	F,M	21 d	Fecundity	260	490	Seki et al. 2002	

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Species	Life Stage	Method	Duration	Endpoint	NOEC (ng/L)	LOEC (ng/L)	Reference	Remarks
Medaka, *Oryzias latipes*	4 mo.	R,U	14 d	Spawning frequency, % fertilized and % hatch.	5	500	Thompson 2000; Tilton et al. 2005	
Cladoceran, *Daphnia magna*	-	R,U	25 d	Embryo production	20,000	100,000	Goto and Hiromi 2003	
Rotifer, *Brachionus calyciflorus*		S,U	72 hr	Ratio of ovigerous/non-ovigerous females	202,000	510,000	Radix et al. 2002	
Rotifer, *Brachionus calyciflorus*		S,U	72 hr	Intrinsic rate population increase r	510,000	1,300,000	Radix et al. 2002	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)								
Fathead minnow, *Pimephales promelas*	>6 mo.	F,M	3 wk	No. spawnings and eggs per spawn	1.5	-	Brian et al. 2007	
Mink frog, *Rana septentrionalis*	fert egg	Field	2 yr	Hatching success	3.2 – 8.9	-	Park and Kidd 2005	
Zebrafish, *Danio rerio* (females)	5-6 mo	R,U	15 d	Sterility in females	5,000	-	Ortiz-Zarragoitia et al. 2006	
Amphipod, *Gammarus pulex*	mixed ages	F, M	100 d	Population growth (total pop. size)	7,600	-	Watts et al. 2002	**Increase** in population size
*Copepod, *Tisbe battagliai*	<24 hr	R,U	21 days	Fecundity	100,000	-	Hutchinson et al. 1999	
*Copepod, *Tisbe battagliai*	<24 hr	R,U	21 days	Reproduction	100,000	-	Pounds et al. 2002	

*Indicates saltwater species.

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Table A.5. Chronic Reproductive Effects of EE2 on Aquatic Animals (Sex Reversal).

Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Remarks
Significant Effects Observed								
Zebrafish, *Danio rerio*	fert egg	F,U	3 mo	Delayed sexual differentiation	-	0.10	Van den Belt et al. 2003	No males at LOEC
Zebrafish, *Danio rerio*	20 dph	R,M	40 d	Male:female sex ratios	-	0.60	Orn et al. 2003	Complete sex reversal at 1.5 ng/L
Fathead minnow, *Pimephales promelas*	40-60 h old	F,M	LC	Male:femal sex ratio	0.32	0.96	Parrott and Blunt 2005	Complete ex. femin. at 3.5 ng/L
Fathead minnow, *Pimephales promelas*	fert. eggs	F,U	60 d	Male:female sex ratio	0.32	1.0	Parrot and Wood 2002	Complete ex. femin. at 3.2 ng/L
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	Male:female sex ratio	-	1.0	Lin and Janz 2006	
Fathead minnow, *Pimephales promelas*	<24 hr	F,M	LC	Sex reversal - all female	0.76	2.8	Länge et al. 2001	Sex ratio at 0.76 ng/L 54:46
Zebrafish, *Danio rerio*	fert egg	F,M	42 d	Male feminization	-	3.0	Fenske et al. 2005	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	125 d	Sex reversal - all female	-	10	Parrot et al. 2003	
Zebrafish, *Danio rerio*	1 dph	R,U	60 d	Complete feminization	-	10	Orn et al 2006	
Zebrafish, *Danio rerio*	1 dph	R,U	60 d	Complete feminization	-	10	Yamani 2004	
Fathead minnow, *Pimephales promelas*	embryo	F,M	114 d	75% female gonads; 15% un-developed	-	12	Bogers et al. 2006b	
Zebrafish, *Danio rerio*	fert egg	R,M	60 d	Complete feminization	-	15	Andersen et al. 2003b	
Medaka, *Oryzias latipes*	1 d	R,M	LC	Male:female sex ratio	2.9	29	Metcalfe et al. 2001	
*Three-spined stickleback, *Gasterosteus aculeatus*	Larvae	R,U	42 d	Sex reversal and intersex	-	50	Hahlbeck et al. 2004a	
Medaka, *Oryzias latipes*	1 d	R,U	2 mo	Sex reversal with ovary	10	100	Scholz and Gutzeit 2000	
Medaka, *Oryzias latipes*	1 d	R,U	60 d	88% female, 2% male, 10% intersex	10	100	Yamani 2004 and Orn et al 2006	
Amphipod, *Gammarus pulex*	mixed ages	F, M	100 d	Male:femal ratio	-	104	Watts et al. 2002	No dose-response >104 ng/L

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Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Remarks
Guppy, *Poecilia reticulate*	< 7 d	F,M	108 d	Male:female sex ratio	44	110	Nielsen and Baatrup 2006	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)								
Green frog, *Rana clamitans*	fert egg	Field	2 yr	Male:female sex ratio	3.2 – 8.9	-	Park and Kidd 2005	
Mink frog, *Rana septentrionalis*	fert egg	Field	2 yr	Male:female sex ratio	3.2 – 8.9	-	Park and Kidd 2005	
Amphipod, *Hyalella azteca*	adult	R,M	10 wk; 2 gen	Male:femal sex ratio	10,000	-	Vandenbergh et al. 2003	
*Copepod, *Tisbe battagliai*	<24 hr	R,U	21 d	Male:female sex ratio	100,000	-	Hutchinson et al. 1999	
Cladoceran, *Daphnia magna*	-	R,U	25 d	Male:female ratio	500,000	-	Goto and Hiromi 2003	

*Indicates saltwater species.

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Table A.6. Chronic Reproductive Effects of EE2 on Aquatic Animals (Intersex).

Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Comments
Significant Effects Observed								
Pearl dace, *Margariscus margarita*	mature	Field	3 yr	Presence of testis-ova	-	3.2 – 8.9	Palace et al. 2006	Edema in ovaries
Fathead minnows, *Pimephales promelas*		Field	3 yr	Presence of testis-ova	-	3.2 – 8.9	Kidd et al. 2007	Testicular malformations
Mink frog, *Rana septentrionalis*	fert eggs	Field	2 yr	Intersex gonads (5 – 12 %)	-	3.2 – 8.9	Park and Kidd 2005	
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Testis-ova in males	1.0	5.0	Zha et al. 2007	No sperm detectable
Fathead minnow, *Pimephales promelas*	egg	F,U	5 d	Ovarian cavities in males (8%)	-	10	Van Aerle et al. 2002	
Fathead minnow, *Pimephales promelas*	5-10 dph	F,U	5 d	Ovarian cavities in males (38%)	-	10	Van Aerle et al. 2002	
Fathead minnow, *Pimephales promelas*	10-15 dph	F,U	5 d	Ovarian cavities in males (64%)	-	10	Van Aerle et al. 2002	
Fathead minnow, *Pimephales promelas*	15-20 dph	F,U	5 d	Ovarian cavities in males (43%)	-	10	Van Aerle et al. 2002	
Fathead minnow, *Pimephales promelas*	egg	F,U	20 d	Ovarian cavities in males (22%)	-	10	Van Aerle et al. 2002	
Medaka, *Oryzias latipes*	1 d	R,M	LC	Sex inversion and testis-ova	2.9	29	Metcalfe et al. 2001	4 of 4 males with TO
*Three-spined stickleback, *Gasterosteus aculeatus*	Larvae	R,U	42 d	Intersexed gonads	-	50	Hahlbeck et al. 2004a	
Medaka, *Oryzias latipes*	6 mo	F,M	21 d	Testis-ova in males (33%)	33	64	Seki et al. 2002	No histological abnormalities in females
Medaka, *Oryzias latipes*	1 d	R,U	2 mo	All males developed an ovary	10	100	Scholz and Gutzeit 2000	No effect on male fertility
Medaka, *Oryzias latipes*	1 d	R,U	60 d	Intersexed gonads (10%)	10	100	Yamani 2004 and Orn et al 2006	
Guppy, *Poecilia reticulata*	< 7 d	F,M	108 d	Feminization of male reproductive ducts	44	110	Nielsen and Baatrup 2006	
Amphipod, *Hyalella azteca*	fert eggs	R,M	2 x gen	Oocyte-like structures in males	23	320	Vandenbergh et al. 2003	
Leopard frog, *Rana pipiens*	Gosner 25	R,M	162 d	Intersex and altered testicular develepment	414	4,140	Mackenzie et al. 2003	

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Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Comments
Wood frog, *Rana sylvatica*	Gosner 25-28	R,M	76 d	Intersex and altered testicular development	-	4,140	Mackenzie et al. 2003	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)								
Green frog, *Rana clamitans*	fert eggs	Field	2 yr	Intersexed gonads	3.2 – 8.9	-	Park and Kidd 2005	
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	Testis-ova	10	-	Lin and Janz 2006	
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	Testis-ova	10	-	Hill and Janz 2003	Excessive carrier solvent; high control mortality
Zebrafish, *Danio rerio*	adult	F,U	21 d	Feminization of testes	25	-	Islinger et al. 2003	

*Indicates saltwater species.

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Table A.7. Chronic Reproductive Effects of EE2 on Aquatic Animals (Sexual Behavior).

Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Remarks
Significant Effects Observed								
*Sand goby, *Pomatoschistus minutus*	juv	F,U	7 mo	Male nesting behavior	-	6	Robinson et al. 2003	High mortality in solvent controls in first month of exposure
Fathead minnow, *Pimephales promelas*	mature	F,M	27 d	Impaired ability to compete and acquire territory	2.0	8.9	Majewski et al. 2002	
*Three-spined stickleback, *Gasterosterus aculeatus*	mature	R,U	12 d	Time spent near nest and glueing frequency, but effect short-lived	-	10	Brian et al. 2006	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)								
Zebrafish, *Danio rerio*	fert egg	F,M	2 x gen	Natural spawning behavior of adult male fish	4.5	-	Nash et al. 2004	Sexually compromised males still actively participated in the spawning act, i.e., chasing females and competing with healthy males
Amphipod, *Gammarus pulex*	3-5 mm	R,M	10 d	Pre-copulatory guarding behavior	3,700,000	-	Watts et al. 2001	Reproductive behavior was only disrupted at high concentrations where it would be unrealistic to attribute effects to and endocrine-mediated process.

Table A.8. Data on Effects of EE2 on Aquatic Animals (Secondary Sexual Characterstics).

Species	Life Stage	Method	Duration	Effect	Event Association	NOEC (ng/L)	LOEC (ng/L)	Reference	Comments
Significant Effects Observed									
Fathead minnow, *Pimephales promelas*	6-11 mo.	F,M	3 wk	Number of male nuptial tubercles	Activational	-	0.80	Pawlowski et al. 2004	
Fathead minnow, *Pimephales promelas*	40-60 h	F,M	LC	Ovipositor size, nuptial tubercles, banding strength	Organizational	0.32	0.96	Parrott and Blunt 2005	
Fathead minnow, *Pimephales promelas*	156 dph	F,M	LC	Nuptial tubercles, banding strength, dorsal fin dot, dorsal fat pad	Activational	0.32	0.96	Parrott and Blunt 2005	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	60 dph	Male sex index: nuptial tubercles, dorsal fat pad, dorsal fin dot, banding strength	Organizational	0.32	1.0	Parrot and Wood 2002	Complete femin. at 3.2 ng/L
Fathead minnow), *Pimephales promelas*	<24 hr	F,M	LC	Secondary sex characteristics – not specified	Organizational	0.76	2.8	Länge et al. 2001	50% sex ratio at 0.76 ng/L
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	60 dph	Development and length of ovipositors	Organizational	1.0	3.2	Parrot and Wood 2002	Complete femin. at 3.5 ng/L
Zebrafish, *Danio rerio*	fert egg	F,M	2 x gen	Coloration and bright anal fin markings	Organizational	-	4.5	Nash et al. 2004	
*Sand goby, *Pomatoschistus minutus*	juv	F,U	7 mo	Delayed and inhibited nuptial coloration in males	Activational	-	6.0	Robinson et al. 2003	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	125 d	Ovipositor size, nuptial tubercles, banding strength	Organizational	-	10	Parrot et al. 2003	
Fathead minnow, *Pimephales promelas*	maturing	F,M	21 d	Number and prominence of nuptial tubercles and dorsal fat pad	Activational	-	11	Filby et al. 2007	
Fathead minnow, *Pimephales promelas*	embryo	F,M	114 d	Number and prominence of nuptial tubercles	Organizational	-	12	Bogers et al. 2006b	
Amphipod, *Hyalella azteca*	fert eggs	R,M	2 x gen	Male second gnathopods	Organizational	-	23	Vandenbergh et al. 2003	No effect >1,000 ng/L
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)									
Fathead minnow, *Pimephales promelas*	>6 mo.	F,M	3 wk	Relative fat pad weight, number of nuptial tubercles, nuptial tubercle prominence	Activational	1.5	-	Brian et al. 2007	
Medaka, *Oryzias latipes*	4 mo	R,U	14 d	Anal and dorsal fin shape	Organizational	500	-	Thompson 2000; Tilton et al. 2005	

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*Indicates saltwater species.

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Table A.9. Chronic Reproductive Effects of EE2 on Aquatic Animals (Vitellogenin).

Species	Life Stage	Method	Duration	Effect	NOEC (ng/L)	LOEC (ng/L)	Reference	Comments
Significant Effects Observed								
Zebrafish, *Danio rerio*	adult males	F,M	40 d	Increased whole-blood VTG level	-	0.50	Nash et al. 2004	
Fathead minnow, *Pimephales promelas*	6-11 mo	F,M	3 wk	Increased plasma VTG levels	-	0.80	Pawlowski et al. 2004	
Rainbow trout, *Oncorhynchus mykiss*	immature female	F,M	14 d	Increased liver *vtg* mRNA expression and plasma VTG	0.21	1.0	Thomas-Jones et al. 2003	
Zebrafish, *Danio rerio*	20 dph	R,M	40 d	Increased whole body VTG levels	-	1.5	Orn et al. 2003	
Zebrafish ,*Danio rerio*	adult male	R,U	21 d	Increased plasma VTG level	-	1.6	Fenske et al. 2001	
Rainbow trout, *Oncorhynchus mykiss*	Adult male	F,M	3 wk	Increased plasma VTG level	-	1.8	Jobling et al. 1996	
Zebrafish, *Danio rerio*	fert egg	F,M	42 d	Increased vitellogenin level	-	3.0	Fenske et al. 2005	
Fathead minnow, *Pimephales promelas*	-	Field	5 mo	Increased plasma VTG levels	-	3.2 – 8.9	Palace et al. 2002 (also see Kidd et al. 2007)	
Pearl dace, *Margariscus margarita*	-	Field	3 yrs	Increased whole body VTG level	-	3.2 – 8.9	Palace et al. 2006	
Zebrafish, *Danio rerio*	adult male	F,M	8 d	Increased whole-body VTG level	2.2	3.6	Rose et al. 2002	EC10 = 0.92 ng/L
Zebrafish, *Danio rerio*	adult females	F,M	40 d	Increased whole-blood VTG level	0.50	4.5	Nash et al. 2004	
Fathead minnow, *Pimephales promelas*	juv	F,M	21 d	Increased whole-body VTG level	2.0	5.0	Panter et al. 2002	
Fathead minnow, *Pimephales promelas*	8 mo	R,M	48 hrs	Increased liver *vtg* levels	2.5	5.0	Biales et al. 2007	
Ide, *Leucisus idus*	juv	F,M	7 d	Increased plasma VTG levels	-	6.0	Allner et al. 1999	
Zebrafish, *Danio rerio*	fert egg	R,M	4 d	Increased whole body VTG level	2.6	7.8	Bogers et al. 2006a	
Zebrafish, *Danio rerio*	adult females	R,M	21 d	Increased plasma VTG level	4.1	8.5	Van den Belt et al. 2004	
Zebrafish, *Danio rerio*	adult males	F,M	24 d	Increased plasma VTG level	-	9.0	Van den Belt et al. 2002	

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Rainbow trout, *Oncorhynchus mykiss*	11 mo	F,M	2 wk	Increased plasm VTG level	0.87	10	Samuelsson et al. 2006	
*Eelpout, *Zoarces viviparus*	adult female	F,M	3 wk	Increased plasma VTG level	5.0	10	Korsgaard et al. 2002	
Fathead minnow), *Pimephales promelas*	<24 hr	F,M	LC	Increased whole body VTG level	2.8	12	Länge et al. 2001	
Zebrafish, *Danio rerio*	adults	F,M	168 hrs	Increased plasma VTG level	-	14	Hoffmann et al. 2006	
Sturgeon, *Acipenser fulvescens*	1 yr	F,M	25 d	Increased plasma VTG levels	-	14	Palace et al. 2001	
Lake trout, *Salvelinus namaycush*	immature	F,M	21 d	Increased plasma VTG level	-	15	Werner et al. 2003	Excessive carrier solvent
*Baltic flounder, *Platichthys flesus*	adult	F,M	21 d	Increased plasma VTG level in male and female fish	-	15	Allen et al. 1999b	
Medaka, *Oryzias latipes*	6 mo.	F,M	21 d	Increased liver Vtg levels	33	64	Seki et al. 2002	
Rainbow trout, *Oncorhynchus mykiss*	juvenile	R,M	14 d	Increased plasma VTG level	10	100	Verslycke et al. 2002	
*Sheepshead minnow, *Cyprinodon variegatus*	male	F,M	16 d	Increased liver *vtg* mRNA expression	24	110	Folmar et al. 2000	
Rainbow trout, *Oncorhynchus mykis*s	mature male	F,M	61 d	Increased plasma VTG levels	-	140	Skillman et al. 2006	
No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)								
Zebrafish, *Danio rerio*	adult males	F,M	310 dpf F1	No effect on whole-blood VTG level	4.5	-	Nash et al. 2004	
Zebrafish, *Danio rerio*	adult females	F,M	310 dpf F1	No effect on whole-blood VTG level	4.5	-	Nash et al. 2004	

*Indicates saltwater species.

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Table A.10. Chronic Effects of EE2 on Aquatic Animals (Other Relevant Endpoints).

Species	Life Stage	Method	Duration	Effect	Concentration (ng/L)	Reference	Remarks
Significant Effects Observed							
Zebrafish , *Danio rerio*	17-20 dpf	R,U	3 d	Enhanced effect on CYP19A2 gene expression	0.30	Kazeto et al. 2004	Excessive carrier solvent
Zebrafish, *Danio rerio*	2 dph	R,U	58 d	Suppression of gametogenesis for males (no testes discernable) and females	1.0	Weber et al 2003	Excessive carrier solvent
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Increased GSI and renal somatic index (RSI) in males	1.0	Zha et al. 2007	
Fathead minnow, *Pimephales promelas*	40-60 h	F,M	LC	Reduced GSI in females	3.5	Parrott and Blunt 2005	
Atlantic salmon, *Salmo salar*	immature	S,U	7 d	Increased AchE and GST activities and lactate content after 3 days, but no effect at 7 days	5.0	Greco et al. 2007	
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Reduced GSI in females	5.0	Zha et al. 2007	
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Increased RSI in females	5.0	Zha et al. 2007	
Medaka, *Oryzias latipes*	4 mo	R,U	14 d	Increased male and female plasma E2 levels	5.0	Thomposn 2000; Tilton et al. 2005	
Fathead minnow, *Pimephales promelas*	6-11 mo	F,M	3 wk	Reduction on male GSI	7.5	Pawlowski et al. 2004	
Zebrafish, *Danio rerio*	Adult female	R,M	21 d	Reduced female ovarian somatic index	8.5	Van den Belt et al. 2004	
Rainbow trout, *Oncorhynchus mykiss*	11 mo	F,M	2 wk	Higher hepatosomatic index (HSI)	10	Samuelsson et al. 2006	
Fathead minnow, *Pimephales promelas*	fert eggs	F,U	125 d	Increased liver somatic index	10	Parrot et al. 2003	
Medaka, *Oryzias latipes*	1 d	R,U	4 mo	In both males and females, significantly increased number of necrotic hepatocytes and kidney tubule cells	10	Weber et al. 2004	
*Baltic flounder, *Platichthys flesus*	adult	F,M	21 d	Increased HSI in males	15	Allen et al. 1999	
Zebrafish, *Danio rerio*	adult male	S,M	21 d	Increased levels of cyp19a2 mRNA (aromatase)	21	Kallivretaki et al. 2006	
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Increased HSI in males	25	Zha et al. 2007	

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Species	Life Stage	Method	Duration	Effect	Concentration (ng/L)	Reference	Remarks
Chinese rare minnow, *Gobiocypris rarus*	7 mo	F,U	28 d	Ovary degeneration in females	25	Zha et al. 2007	
Zebrafish, Danio rerio	adult male	F,M	7 d	Decreased testrosterone and 11-ketotestosterone levels	26	Andersen et al. 2006	
Atlantic salmon, *Salmo salar*	immature	S,U	72 hr	Induced expression of brain P450 Aromatase	50	Lyssimachou et al. 2006	
Sturgeon, *Acipenser fulvescens*	1 yr	F,M	25 d	Increased plasma Vit E, A1 and A2; Decreased Vit E and A in kidney	60	Palace et al. 2001	
*Sheepshead minnow, *Cyprinodon variegatus*	juv	F,M	PLC	Increased pathological condition of kidneys	120	Zillioux et al. 2001	Fish survived to reproduction
Rainbow trout, *Oncorhynchus mykiss*	mature male	F,M	3 wk	Changed gene expression profile	130	Hook et al. 2007	
Zebrafish , Danio rerio	18-21 d	R,U	72 hr	Stimulated expression of Cytochrome P450 aromatase (Aro-B)	300	Le Page et al. 2006	
Medaka, *Oryzias latipes*	mature	R,U	14 d	Induced ER protein and aromatase activity	500	Contractor et al. 2004	
Medaka, *Oryzias latipes*	adult	R,U	14 d	Increased hepatic estrogen receptor (ER)	500	Thompson 2000	
Medaka, *Oryzias latipes*	4 mo.	R,U	14 d	Decreased female and male GSI	500	Thompson 2000; Tilton et al. 2005	
African clawed frog, *Xenopus laevis*	adult	R,U	4 wk	Reduced Leutinizing hormone B mRNA expression	3,000	Urbatzka et al. 2006	
African clawed frog, Xenopus laevis	adult	R,U	4 wk	Reduced testosterone levels in both sexes	3,000	Urbatzka et al. 2007	
African clawed frog, Xenopus laevis	adult	R,U	4 wk	Reduced E2 level in females	3,000	Urbatzka et al. 2007	
Midge, *Chironomus riparius*	4th instar	S,U	24 h	Increased expression of heat shock proteins	8,000	Lee et al. 2006	
Medaka, *Oryzias latipes*	mature male	R,U	6 d	Increased mRNA expression of liver choriogenin L	10,000	Lee et al. 2002b	
Medaka, *Oryzias latipes*	mature male	R,U	6 d	Increased mRNA expression of liver choriogenin H levels	20,000	Lee et al. 2002b	
Medaka, *Oryzias latipes*	mature male	R,U	6 d	Increased mRNA expression of liver choriogenin H levels	20,000	Lee et al. 2002a	
Medaka, *Oryzias latipes*	juv	R,U	6 d	Increased mRNA expression of whole body Choriogenic H	50,000	Lee et al. 2002a	

No Signficiant Effects Observed (NOEC Equals Highest Test Concentration)

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Species	Life Stage	Method	Duration	Effect	Concentration (ng/L)	Reference	Remarks
*Sand goby, *Pomatoschistus minutus*	juv	F,U	7 mo	No effect on GSI in males or females	6.0	Robinson et al. 2003	
Rainbow trout, *Oncorhynchus mykiss*	juvenile	R,M	14 d	No effect on GSI or HSI	100	Verslycke et al. 2002	
African clawed frog, *Xenopus laevis*	adult	R,U	4 wk	No effect on Gonadotropin Releasing Hormone mRNA expression	3,000	Urbatzka et al. 2006	

*Indicates saltwater species.

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2020 TR LANL-01818

Exhibit 85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER

MEMORANDUM

SUBJECT: Recommendations from the PFAS NPDES Regional Coordinators Committee
Interim Strategy for Per- and Polyfluoroalkyl Substances in Federally Issued National Pollutant Discharge Elimination System Permits

FROM: David P. Ross
Assistant Administrator

DAVID ROSS
Digitally signed by DAVID ROSS
Date: 2020.11.22 22:43:00 -05'00'

TO: Regional Administrators
Regions 1–10

The purpose of this memorandum is to transmit recommendations developed by a workgroup comprised of U.S. Environmental Protection Agency (EPA or Agency) Headquarters and Regional contacts. By transmitting these recommendations, I am also seeking your support in ensuring the recommendations encompassed in this interim strategy for Per- and Polyfluoroalkyl Substances (PFAS) in federally issued National Pollutant Discharge Elimination System (NPDES) permits are implemented.

EPA's Office of Water (OW) is currently leading multiple actions in the PFAS Action Plan that will help the Agency better understand and effectively manage risk from exposure to PFAS. These OW-led actions include developing analytical methods for detecting PFAS in drinking water and other environmental media, evaluating PFAS treatment techniques, understanding PFAS exposure from various environmental media, and evaluating statutory and regulatory mechanisms to manage adverse human health and environmental impacts from PFAS exposure. OW has made outstanding progress in each of these areas since the Action Plan was announced in February 2019. Among the important work underway are efforts to address point source discharges of PFAS in accordance with Clean Water Act (CWA) Section 402 NPDES permits.

While OW's work is advancing, a need for an interim strategy to address point source discharges of PFAS in EPA-issued NPDES permits has been identified. On February 6, 2020, the workgroup was established to develop an interim NPDES permitting strategy to address PFAS in EPA-issued CWA Section 402 permits. The workgroup was charged with exploring options on how to address these pollutants while the CWA framework for potentially regulating PFAS discharges pursuant to the NPDES program is under development. The workgroup's goal was to develop a strategy that would serve to guide the Agency's CWA NPDES permitting approach on an interim basis across the EPA Regions as informed by input from our state partners. Each of the ten EPA Regions appointed a representative to the workgroup.

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To develop potential recommendations for an interim PFAS NPDES strategy, the workgroup conducted a thorough review of the NPDES permitting process, with a specific focus on PFAS in the context of permitting. This included examining CWA Section 402 authorities and permit writing practices to understand where unregulated contaminants, such as PFAS, may fit into the permit development process; analyzing existing state-issued NPDES permits with PFAS monitoring requirements (identified through EPA's NPDES Integrated Compliance Information System (ICIS)) to understand the prescribed analytical methods for detecting PFAS, monitoring frequency, and detection benchmarks in current permits; and obtaining input and perspectives from state partners.

Workgroup Recommendations:

1) **Include permit requirements for phased-in monitoring and best management practices, as appropriate, taking into consideration when PFAS are expected to be present in point source wastewater discharges.**

The workgroup recommends that EPA NPDES permit writers consider incorporating permit requirements for monitoring PFAS at facilities where PFAS are expected to be present in point source wastewater discharges. The PFAS that could be considered for monitoring are those that will be part of EPA's multi-lab validated wastewater analytical method. This recommendation is consistent with EPA's 2010 NPDES Permit Writers Manual,[1] Section 6.2.1.5, "Pollutants Otherwise Expected to be Present in the Discharge." This section of the NPDES Permit Writer's Manual notes that there may be pollutants for which neither the discharger nor the permitting authority have monitoring data, but because of the raw materials stored or used at the facility, products or byproducts of the facility operation, or available data and information from similar facilities, the permit writer has a strong basis for expecting that the pollutant could be present in the discharge.

The workgroup also recognizes the need for reliable and accurate analytical methods and resulting data when considering the incorporation of monitoring provisions into NPDES permit requirements. The workgroup recommends a phased approach to any potential PFAS monitoring provision, such that monitoring requirements are triggered at a time after EPA's multi-lab validated methods are made available to the public. OW expects to have a multi-lab validated PFAS analytical method available for detecting certain PFAS in wastewater and several other matrices in 2021. EPA water quality methods are developed with particular attention to accuracy and precision and have been through single- and multi-lab validation. Generally, the permitting authority requires the use of methods approved at 40 CFR Part 136 for compliance with such monitoring requirements. If no approved methods are available at 40 CFR Part 136, then the permitting authority has discretion to specify the use of suitable methods.

The workgroup also recommends permit writers consider and incorporate best management practices when appropriate to control or abate the discharge of PFAS where authorized for both direct and indirect dischargers.[2]

[1] *See* EPA-833-K-10-001, September 2010.

[2] For industrial NPDES and stormwater NPDES discharges, 40 CFR 122.44(k). For POTW NPDES discharges, 40 CFR 403.8(f)(1)(iii)(B)(3).

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2) **Include permit requirements for phased-in monitoring and stormwater pollutant control, as appropriate, taking into consideration when PFAS are expected to be present in stormwater discharges.**

The workgroup recommends consideration of pollutant control measures in municipal separate storm sewer system (MS4) and industrial stormwater permits when PFAS are expected to be present in stormwater discharges. In addition, the workgroup recommends a phased approach to incorporating monitoring in these permits, as described above, when deemed appropriate by the permit writer.

MS4 permits generally require permittees to implement traditional stormwater controls necessary to reduce the discharge of pollutants from MS4s to the "maximum extent practicable" and to make progress towards achieving other water quality objectives.[3,4] MS4 permits typically require controls that focus on programs to reduce pollutant discharges through public education and outreach, illicit discharge detection and elimination, construction site stormwater runoff control, and pollution prevention measures. Additional requirements may be necessary to address specific pollutants of concern for specific water quality problems in receiving waters. In the same way, where PFAS are pollutants of concern, NPDES authorities may consider using these traditional controls to reduce PFAS discharges in stormwater.

Industrial stormwater permits generally require permittees to implement stormwater controls necessary to reduce the discharge of pollutants from industrial activities and to achieve applicable water quality standards. Typically, industrial permittees develop stormwater pollution prevention plans (SWPPPs), implement stormwater control measures to meet permit effluent limits, and conduct inspections and monitoring, where applicable. Where PFAS are pollutants of concern, NPDES authorities may consider using these general types of controls to reduce PFAS discharges in stormwater.

3) **Information sharing on permitting practices and the development of a permitting compendium, an information sharing platform, and continuation of the workgroup.**

Knowledge sharing and development of a common understanding of issues is helpful for emerging permitting topics in the NPDES program. Such actions help to establish best practices and communities of technical knowledge. The workgroup recommends building on the work that has already started on PFAS-specific communication, knowledge sharing, capacity-building, and training at the federal and state levels.

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[3] CWA Section 402(p)(3)(B)(iii) provides that "[p]ermits for discharges from municipal storm sewers shall require controls to reduce the discharge of pollutants to the maximum extent practicable including management practices, control techniques and system, design and engineering methods, and such other provisions as the Administrator or the State determines appropriate for the control of such pollutants." The Phase II stormwater regulations at 40 CFR 122.34(a) further specify that small MS4s permits "must include permit terms and conditions to reduce the discharge of pollutants from the MS4 to the maximum extent practicable (MEP), to protect water quality, and to satisfy the appropriate water quality requirements of the Clean Water Act."

[4] To recognize the importance of flexibility in establishing conditions based on the "maximum extent practicable" (MEP) standard and of optimizing reductions in stormwater pollutants on a location-by-location basis, "EPA has intentionally not provided a precise definition of MEP to allow maximum flexibility in MS4 permitting." 64 FR 68754 (Dec. 8, 1999). In establishing MEP-based permit requirements, EPA suggests consideration of "such factors as conditions of receiving waters, specific local concerns, and other aspects included in a comprehensive watershed plan. Other factors may include MS4 size, climate, implementation schedules, current ability to finance the program, beneficial uses of receiving water, hydrology, geology, and capacity to perform operation and maintenance." *Ibid*.

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Permitting Compendium

The NPDES program has promoted the development and publishing of permitting compendia to share information. These compendia present examples of different permitting approaches that EPA identifies in a nationwide review of NPDES permits in a specific programmatic area. Current permitting compendia are located at https://www.epa.gov/npdes/municipal-sources-resources. A PFAS permitting compendium would build on the initial evaluation of permits conducted to date and would serve as a source of information for states and EPA to learn about practices being adopted in NPDES permits to address PFAS across the nation. Consistent with other compendia, EPA would update the document as new information is received and make it available on its website.

Information Sharing Platform

As PFAS information relevant to the NPDES program becomes available, the workgroup believes it would be beneficial to establish a mechanism for information sharing to facilitate frequent and timely communication with the states and our partners. The workgroup recommends that OW encourage utilizing the EPA's NPDES Permit Writers' Clearinghouse to share information on PFAS relevant to permitting.[5] The Clearinghouse is a searchable database containing resources such as permits, templates, and webinars that are shared by NPDES authorities. It is primarily populated and used by permitting authorities and practitioners.

Continuation of the Workgroup

The NPDES PFAS workgroup has provided a forum for robust discussion on PFAS in the context of CWA Section 402 permitting. This resulted in valuable insights from key stakeholders at the EPA regional and state levels. As work on PFAS evolves, this workgroup can serve as an ongoing source of NPDES permitting knowledge and practice through continued collaboration with state permitting authorities.

The workgroup recommends PFAS-specific communication, knowledge sharing, capacity-building, and training opportunities through the following deliverables:

Deliverable	Timeline
Build-out relevant NPDES permitting information on the EPA PFAS website and NPDES Permit Writers' Clearinghouse.	June 2021
Publish a PFAS permitting compendium that provides examples of permit conditions that have been developed and issued by states and EPA.	Third Quarter 2021
Host quarterly meetings of the Regional Coordinators workgroup.	Beginning January 2021
Broadcast two webinars for states and EPA Regions on relevant PFAS topics.	First Quarter 2021
Work with the Association of Clean Water Administrators (ACWA) to organize 2nd state listening session.[6]	First Quarter 2021

[5] https://ofmpub.epa.gov/apex/pwc/f?p=206:1:186468836250::NO:::

[6] The first state listening session was held on March 18, 2020.

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cc: Andrew Sawyers, Director, Office of Wastewater Management
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Jennifer McLain, Director, Office of Groundwater and Drinking Water
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2020 TR LANL-01824

Exhibit 86

COLORADO
Water Quality
Control Commission
Department of Public Health & Environment

Water Quality Control Commission
Policy 20-1
Policy for Interpreting the Narrative Water Quality Standards for Per- and Polyfluoroalkyl Substances (PFAS)

5 CCR 1002-31, Section 31.11(1)(a)(iv)
and
5 CCR 1002-41, Section 41.5(A)(1)

Approved: July 14, 2020
Expires: July 31, 2025

2020 TR LANL-01826

Water Quality Control Commission
Policy 20-1 Policy for Interpreting the Narrative
Water Quality Standards for Per- and
Polyfluoroalkyl Substances (PFAS)

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I. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a family of human-made chemicals with over 5,000 compounds that have been used for decades in products like food packaging, carpets, non-stick products, other household items, medical supplies, and firefighting foam due to their ability to resist heat, oil, stains, grease, and water. Health effects from PFAS may include pregnancy complications, developmental effects, and liver and kidney effects.[1] Additionally, there is limited evidence linking exposure to PFAS to certain cancers[1]. PFAS have been detected across the United States and in Colorado in several different locations, including Security, Widefield, Fountain, Commerce City, and two fire districts near Boulder. In 2018 the Water Quality Control Commission (commission) adopted a site-specific groundwater standard in El Paso County. In 2018, Colorado's Solid and Hazardous Waste Commission added two PFAS, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), to the hazardous constituent list in Section 261, Appendix VIII. Additionally, the Colorado Department of Public Health and Environment (department) is implementing an action plan to address PFAS and protect public health. As part of this action plan, the commission is adopting this policy that interprets the narrative standard provisions in the commission's Regulations No. 31.11(1)(a)(iv) and No. 41.5(A)(1) for PFAS.

Due to the presence of PFAS in some Colorado waters, there will be circumstances in which the Water Quality Control Division (division) needs to make decisions about potential regulatory actions, whether a policy interpreting narrative water quality standards for PFAS is adopted or not. It is the commission's intent in adopting this policy to help provide consistency and transparency in how PFAS is addressed. The commission notes that this policy relies on the division's existing legal authority (rather than providing new authority) to implement and interpret the narrative standard provisions in the commission's Regulations No. 31.11(1)(a)(iv) and No. 41.5(A)(1) for PFAS.

This policy will have the same effect as other commission and division policies. In other words, it will assist the division in implementing the commission's water quality standards and regulations. This policy is not intended to, and does not, create any new authority for the division beyond that which exists under current law. Moreover, this policy is not intended, and should not be interpreted, to limit any options that may be considered or adopted by the commission in future rulemaking proceedings. Therefore, this policy statement can, and will, be modified over time as warranted by future policy or rulemaking decisions.

[1] https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf

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II. Central Concepts of this Policy for Interpreting the Narrative Standards for PFAS

Section 31.11(1)(a)(iv) of the commission's regulations states, in relevant part, that "state surface waters shall be free from substances attributable to human-caused point source or nonpoint source discharge in amounts, concentrations or combinations which are harmful to the beneficial uses or toxic to humans, animals, plants, or aquatic life." Section 41.5(A)(1) states that "Groundwater shall be free from pollutants not listed in the tables referred to in section 41.5(B), which alone or in combination with other substances, are in concentrations shown to be...Carcinogenic, mutagenic, teratogenic, or toxic to human beings, and/or,...A danger to the public health, safety, or welfare."

The commission anticipates that this interpretation of the narrative standards for PFAS will provide information useful to the division and the SB89-181 groundwater implementing agencies as they implement their regulations that rely on the narrative standards in Regulations No. 31.11(1)(a)(iv) and No. 41.5(A)(1) to protect waters intended for drinking water for their beneficial use. The groundwater implementing agencies include: Division of Reclamation, Mining and Safety, Colorado Oil and Gas Conservation Commission, Division of Oil and Public Safety, Hazardous Materials and Waste Management Division (HMWMD), and Division of Water Resources.

This policy does not directly implement any portions of the division's Safe Drinking Water Act (SDWA) responsibilities or establish state drinking water standards for any PFAS. However, this policy could be used in cleanup actions for drinking water sources contaminated by PFAS and for the protection of drinking water sources.

III. History and Anticipated Path Forward for PFAS in Colorado

The 1996 SDWA amendments require that once every five years the U.S. Environmental Protection Agency (EPA) issue a new list of no more than 30 unregulated contaminants to be monitored by public water systems. This is known as the Unregulated Contaminant Monitoring Rule. The third Unregulated Contaminant Monitoring Rule (UCMR 3) was published on May 2, 2012 and required public water systems to monitor between 2013 and 2015 for, among other contaminants, two types of PFAS: PFOA and PFOS. As a result of this monitoring, PFOA and PFOS were detected across the United States, and in Colorado in the aquifers serving Security, Widefield, and Fountain water districts.

In 2009, EPA developed provisional health advisories for PFOA and PFOS to assess potential risk from exposure to these chemicals through drinking water. Subsequently, EPA conducted an updated evaluation of literature on human health effects associated with PFOA

and PFOS and issued draft health effects documents in 2014 for public comment and external peer review. In May 2016, the EPA released a revised lifetime health advisory of 70 ng/L for individual, or combined, PFOA and PFOS concentrations. Health advisories are not regulatory standards, and there is currently no national PFAS numeric regulatory standard. On April 9, 2018, the commission adopted a site-specific groundwater quality standard of 70 ng/L for combined PFOA and PFOS. The intent of this standard is to provide a cleanup goal for the contaminated aquifer in El Paso County, while also working to avoid additional contamination of this aquifer, which serves as a drinking water source for surrounding communities. This site-specific groundwater quality standard applies to Specified Area 7 in Regulation No. 42, which includes aquifers used as drinking water supplies by the City of Fountain, the Security Water District, the Widefield Water and Sanitation District, and the Stratmoor Hills Water District. A detailed description of this area is included in Regulation No. 42. The site-specific groundwater quality standard became effective on June 30, 2018.

The department has an action plan for addressing PFAS contamination in Colorado, which includes steps to minimize the risk of additional contamination and respond to communities where these chemicals are found at levels that could affect health. The department has several actions planned in order to protect Coloradans from the negative health consequences of PFAS: conduct a survey of fire departments and their use of PFAS containing foam as directed by legislation in HB19-1279, develop an inventory of where PFAS have been found or believed to have been released to understand the extent of contamination, consider new statewide regulatory standards for drinking water, surface water and groundwater, ensure proper disposal of contaminated materials, study health impacts, and continue to engage at a national level and learn from other states.

With $500,000 awarded from the state legislature, the department facilitated the sampling of 400 water systems and 15 firefighting districts as well as 152 groundwater sources and 71 surface water sources. The sampling represents approximately half of the community drinking water systems in the state serving around three-quarters of the population. 415 entities tested treated drinking water and/or source water, or untreated water that eventually is treated to become drinking water, and no tap water exceeded the EPA health advisory. Four entities had groundwater sources with sample results that exceeded the EPA health advisory. Three of the four entities already tested for the chemicals in previous years and have notified the public of those results: Stratmoor Hills Water and Sanitation District and Security Water and Sanitation District located in El Paso County, and Sugarloaf fire district located in Boulder County. The entities are either not using that source water or treating the water to remove the chemicals before using it as drinking water. The additional entity is Fourmile Fire District, located in Teller County. The department, fire district, and local public health agency are examining the geographical area to see if any residents living nearby may be impacted. Residents that live near the Four Mile station have been notified of the results. All of the samples collected at surface water sources had some detectable level

of the chemicals. The sample collected at the mouth of Sand Creek in Commerce City was above the EPA drinking water health advisory.

There are federal efforts to address PFAS and to protect public health. EPA has identified PFAS reduction efforts under the Toxic Substances Control Act and the 2006 voluntary stewardship program for PFOA and related chemicals. This program was developed at a time when EPA lacked the authority to evaluate existing chemical legacy uses under the act, authority that was later granted through the 2016 Lautenberg Chemical Safety Act. PFOS was not included in the program, since it was no longer in production in the US at the time.

EPA's PFAS Action Plan, issued February 2019, outlines concrete steps the agency is taking to address PFAS and to protect public health using regulatory and programmatic tools. In February 2020, EPA announced its proposed regulatory determination to regulate PFOA and PFOS in drinking water. The EPA is working on finalizing draft toxicity assessments for hexafluoropropylene oxide dimer acid or 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propionic acid (GenX) and perfluorobutanesulfonic acid (PFBS) and will develop additional PFAS toxicity values for perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA). In December 2019, EPA finalized its interim recommendations for addressing groundwater contaminated with PFAS. Specifically, EPA recommends using a screening level of 40 ng/L to determine if PFOA and/or PFOS is present at a site and may warrant further attention and using EPA's health advisory as the preliminary remediation goal for contaminated groundwater that is a current or potential source of drinking water, where no state or tribal maximum contaminant level or other applicable or relevant and appropriate requirements (ARARs) are available or sufficiently protective. In December 2019, EPA began accepting public comment to gather information for use in a potential rulemaking to add certain PFAS to the Toxics Release Inventory (TRI) toxic chemical list under Section 313 of the Emergency Planning and Community Right-to-Know Act. In June 2020, the EPA announced that it is barring companies from manufacturing, processing or importing "significant new uses" of products containing long-chain PFAS, without explicit EPA approval. The new rule applies to ski wax, carpets, furniture and a range of other consumer products.[2]

The National Defense Authorization Act PFAS provisions will require: addition of 172 PFAS to the EPA TRI list and subject to TRI reporting requirements for Reporting Year 2020 (this is independent of the TRI regulatory work EPA already had underway and in February 2020, EPA updated their TRI list from 160 PFAS to 172 PFAS), nationwide drinking water monitoring for PFAS as part of UCMR 5, EPA to finalize by June of 2020 a Significant New Use Rule for Long-Chain PFAS under the Toxic Substances Control Act, and EPA to publish PFAS destruction and disposal interim guidance within a year. These provisions authorize funding

[2] www.epa.gov/sites/production/files/2020-06/documents/10010-44_prepubcopy_fr_doc_epa_admin_esign_2020-06-22final.pdf

for SDWA grants to public water systems to address PFAS and require the U.S. Geological Survey to develop methods for detecting PFAS in the environment and carry out nationwide sampling to determine PFAS concentrations in estuaries, lakes, streams, springs, wells, wetlands, rivers, aquifers and soils. In the absence of federal standards, multiple states have established drinking water, surface water, and groundwater standards to address PFAS contamination. The Interstate Technology Regulatory Council (ITRC) maintains a list of states that have developed draft, proposed, or final health-based regulatory and/or guidance values for several PFAS in drinking water, groundwater, or surface water. These values often differ from the EPA health advisory or from state-to-state given various legislative and scientific considerations. Several states have proposed or adopted both regulatory and non-regulatory values for PFAS in drinking water that are much lower than EPA's health advisory.

Although there is progress being made at the federal level, the commission has determined that adopting Policy 20-1 is an appropriate step to address this complicated public health issue. The commission anticipates that this policy will result in consistent monitoring results around the state, help the commission and department better understand the prevalence and potential exposure of PFAS throughout the state, and reduce exposure to PFAS. The policy will be implemented as part of the department's PFAS Action Plan which is focused on reducing exposure to PFAS.

IV. Policy Applicability

The division should consider this policy for all existing and future, domestic and non-domestic, surface water and groundwater discharge permits issued by the division. In addition, the policy can be considered by the SB89-181 groundwater implementing agencies in their efforts to protect groundwater quality. Finally, the division could consider this policy when reviewing drinking water monitoring results for PFAS to evaluate the potential for human health effects.

V. Overview of Approach Interpreting the Narrative Standards for PFAS

The commission's approach for interpreting the narrative standards for PFAS includes laboratory method and sampling considerations, translating the narrative standards for PFAS, cleanup of contaminated groundwater considerations, implementation in Colorado Discharge System Permits, and Colorado's impaired water list considerations. The commission's approach is consistent with the division's and commission's previous approaches to addressing and implementing narrative standards. These approaches have considered identifying the methods for deriving chemical-specific values using available toxicity data and statements or procedures describing how the division or commission intend to use the chemical specific values to manage water quality through permitting and the impaired water lists.

In applying the translation levels in permitting or other regulatory activities, it is the commission's intent that the division have flexibility. Specifically, in individual circumstances that present material information that differs from the assumptions underlying this policy, the commission understands that the division may exercise its professional judgment to implement the narrative standard in a manner that may differ from the specifics of this policy.

VI. Laboratory Method and Sampling Considerations

There are two EPA validated analytical methods for measuring PFAS in potable (drinking) waters (Methods 533 and 537.1). However, there are currently no analytical methods for analyzing PFAS in wastewaters (non-potable) that are approved for Clean Water Act monitoring per 40 Code of Federal Regulations (CFR) Part 136 (Appendix B). Therefore, the department surveyed analytical laboratories nationwide to obtain information on available PFAS analytical services. Laboratories were surveyed to determine their capabilities to analyze the 25 PFAS presented in Table 1 in wastewater, as these constituents comprise the list of constituents anticipated to be included in the upcoming EPA 1600 series method for analyzing PFAS in non-potable waters. Based on the results from this survey, there are several laboratories capable of analyzing the 25 constituents included in Table 1 at the "PFAS quantification limits (PFAS QLs)" listed in Table 1 and the department should consider the following analytical method stipulations in approving a method in the absence of an EPA approved method for wastewater:

- The laboratory selected should be able to perform analysis on wastewater (non-potable) matrices using a method that is compliant with the requirements set forth in the Department of Defense (DoD) Quality Systems Manual (QSM) for Environmental Laboratories (DoD QSM 5.1 or later [Table B-15: Per- and Polyfluoroalkyl Substances (PFAS) Using Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) With Isotope Dilution or Internal Standard Quantification in Matrices Other Than Drinking Water]).[3] Any 40 CFR Part 136 (Appendix B) approved method for analyzing PFAS in wastewater that becomes available in the future would replace the current analytical method recommendations included in this policy. The commission anticipates that a 40 CFR Part 136 method will become available by the time this policy expires. However, if a method does not become available, the commission recommends that the analytical method stipulations included in this policy be reviewed at the next routine review of this policy.

- In addition to the method requirements provided above, the laboratory selected should be able to analyze, at a minimum, for the list of (25) PFAS shown in Table

[3] https://www.denix.osd.mil/edqw/documents/manuals/qsm-version-5-3-final/, please refer to the most up-to-date version available.

1. The laboratory should also be able to quantify those PFAS at or below the laboratory PFAS QLs shown in Table 1. The PFAS QLs refer to the lowest concentration of an analyte that can be accurately and precisely quantified using a given method, as determined by the laboratory. If the laboratory selected is capable of achieving a quantification limit for a specific PFAS that is lower than the PFAS QL shown in Table 1, analytical results should be reported to the department relative to the lower laboratory quantification limit , and not reported as "less than" the PFAS QLs provided in Table 1.

Table 1 PFAS and PFAS Quantification Limits for Laboratory Analysis

Acronym	Chemical Name	CAS #	PFAS Quantification Limits (ng/L)
4:2 FTS	Fluorotelomer sulphonic acid 4:2	757124-72-4	≤20
6:2 FTS	Fluorotelomer sulphonic acid 6:2	27619-97-2	≤55
8:2 FTS	Fluorotelomer sulphonic acid 8:2	39108-34-4	≤20
Gen-X (or HFPO-DA or HFPA-DA)	Hexafluoropropylene oxide dimer acid or 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propionic acid	13252-13-6	≤6
NEtFOSAA	N-Ethyl perfluorooctanesulfonamidoacetic acid OR 2-(Nethylperfluorooctanesulfonamido) acetic acid	2991-50-6	≤20
NMeFOSAA	N-methylperfluorooctane sulfonamidoacetic acid OR 2-(N-methyl-perfluorooctane sulfonamido) acetic acid	2355-31-9	≤20
PFBA	Perfluorobutanoic acid	375-22-4	≤7
PFBS	Perfluorobutanesulfonic acid	375-73-5	≤2
PFDA	Perfluorodecanoic acid	335-76-2	≤2
PFDoA	Perfluorododecanoic acid	307-55-1	≤2
PFDS	Perfluorodecanesulfonic acid	335-77-3	≤2
PFHpA	Perfluoroheptanoic Acid	375-85-9	≤3

PFHpS	Perfluoroheptane sulfonate, Perfluoroheptane sulfonic acid	375-92-8	≤2
PFHxA	Perfluorohexanoic acid	307-24-4	≤10
PFHxS	Perfluorohexanesulfonic acid	355-46-4	≤2
PFNA	Perfluorononanoic acid	375-95-1	≤2
PFNS	Perfluorononanesulfonic acid	68259-12-1	≤2
PFOA	Perfluorooctanoic acid	335-67-1	≤2
PFOS	Perfluorooctanesulfonic acid	1763-23-1	≤2
PFOSA (or FOSA)	Perfluorooctanesulfonamide	754-91-6	≤2
PFPeA	Perfluoropentanoic acid	2706-90-3	≤3
PFPeS	Perfluoropentanesulfonic acid	2706-91-4	≤2
PFTeDA (or PFTA or PFTeA)	Perfluorotetradecanoic acid	376-06-7	≤2
PFTrDA (or RFTriA)	Perfluorotridecanoic acid	72629-94-8	≤2
PFUnA (or PFUdA)	Perfluoroundecanoic acid	2058-94-8	≤2

The accuracy of sampling results depends on using appropriate sampling techniques. Due to the widespread use of PFAS, many materials normally used to perform field sample collection and laboratory analysis contain PFAS (e.g. tubing, sample containers, and sampling tools made of polytetrafluoroethylene). Since these products can contain PFAS, they cannot be used in sampling for PFAS. Additionally, cross-contamination of samples could occur through the use of consumer goods containing PFAS at the sample site. Thus, the use of appropriate field sampling and laboratory protocols is important for ensuring PFAS testing results reflect actual PFAS levels in the analyzed media. Furthermore, collection and analysis of quality control samples are important for PFAS analyses because of very low detection limits and widespread commercial use (historical and current) of PFAS containing products. Entities collecting monitoring samples for PFAS should work closely with the analytical laboratory selected to determine proper sampling equipment. The Interstate Technology and Regulatory Council provides useful information regarding PFAS sampling precautions in Section

3 of their factsheet for PFAS Site Characterization.[4] In addition, the Michigan Department of Environmental Quality and California State Water Quality Control Board, amongst others have developed PFAS sampling guidelines.[5,6]

VII. Translating the Narrative Standards for PFAS

The commission translated the narrative standards for a subset of the PFAS included on the monitoring list: PFOA, PFOS, PFNA, PFHxS, and PFBS. These translation levels are chemical specific values that are based on available toxicity data at the federal level. The translation levels were developed using results from federally-derived consensus findings regarding the toxicity of these constituents. PFAS outlined in the Table 1 monitoring list that could degrade or transform into PFOA, PFOS, PFNA, PFHxS, or PFBS were also identified. These are listed in Table 2 and will be referred to hereafter as "parent constituents". It is the commission's interpretation of the narrative standard that concentrations of measured parent constituents should be first multiplied by the ratio of the degradate's (i.e., PFOA, PFOS, PFNA, PFHxS, or PFBS) molecular weight over the parent's molecular weight, and then added to the concentration of the degradate measured, before comparing to the translation level. The commission recommends that these translation levels be reviewed on a regular basis and as needed based on evolving science.

[4] https://pfas-1.itrcweb.org/wp-content/uploads/2018/03/pfas_fact_sheet_site_characterization_3_15_18.pdf
[5] https://www.michigan.gov/documents/pfasresponse/General_PFAS_Sampling_Guidance_634597_7.pdf
[6] https://www.waterboards.ca.gov/pfas/docs/march_pfas_sampling_guidelines.pdf

Table 2 Parent Constituents from the Monitoring List (Table 1) that Could Degrade or Transform to PFOA, PFOS, PFNA, PFHxS, or PFBS

PFAS Parent Constituent	PFAS Parent Constituent Molecular Weight (g/mol)	PFAS Degradate Constituent (i.e., PFOA, PFOS, PFHxS or PFNA)	PFAS Degradate Constituent Molecular Weight (g/mol)	Concentration adjustment for Parent Constituent (4th column/2nd column)	Technical Source used to Identify Parent Compound
NEtFOSAA	585.24	PFOS	500.13	0.85	Buck et al. 2011*
NMeFOSAA	571.21	PFOS	500.13	0.88	Buck et al. 2011*
PFOSA/FOSA	499.15	PFOS	500.13	1.0	Buck et al. 2011*
8:2 FTS	528.18	PFOA	414.07	0.78	Liu et al. 2013**

*Buck et al. (2011) Perfluoroalkyl and Polyfluoroalkyl Substances in the Environment: Terminology, Classification, and Origins. Integrated Environmental Assessment and Management. Vol 7, Numb 4. p. 513-541.
**Liu et al. (2013) Microbial degradation of polyfluoroalkyl chemicals in the environment: A review. Environment International. 61, p. 98-114.

For PFOA, PFOS, and PFNA, it is the commission's interpretation of the narrative standard that a translation level of 70 ng/L applies (Table 3). This translation level applies to each of these constituents individually and to the sum of the three constituents plus the four parent constituents included in Table 2 (i.e., PFOA+PFOS+PFNA+NEtFOSAA (adjusted)+NMeFOSAA (adjusted)+ PFOSA/FOSA (adjusted)+8:2 FTS (adjusted)). This translation level is based on the 2016 EPA health advisory for PFOA and PFOS, which established a non-regulatory lifetime health advisory concentration of 70 ng/L for PFOS and PFOA (individually or combined). These health advisories identify the concentration of PFOA and PFOS in drinking water at which adverse health effects are not anticipated to occur over a lifetime, and were based on the best science available at the time of completion. EPA based these health advisories on the protection of lactating women who often drink more water than other people and can transfer PFAS to their nursing infants through breast milk. In the development of the health advisories, EPA took into consideration sources of exposure to PFOA and PFOS other than drinking water, including: air, food, dust, and consumer products. EPA used a relative source contribution of 20%, which allows for other PFOA and PFOS exposure sources (e.g., dust, diet, air) to make up 80% of the reference dose. Both the health advisory for PFOA and the health advisory for PFOS were developed using a reference dose derived from a developmental toxicity study in animals (mice for PFOA and rats for PFOS). The critical effects observed for PFOA included reduced ossification in proximal phalanges and accelerated puberty in male pups following exposure during gestation and lactation. The critical effect for PFOS was decreased pup body weight following exposure during gestation and lactation. Per the health advisories, EPA relies on EPA risk assessment guidelines that reflect that a single exposure to a developmental toxin at a critical time in development can

produce an adverse effect.[7,8,9] In addition, EPA states that short-term exposure to PFAS can result in a body burden that persists for years and can increase with additional exposures. Thus, EPA recommends that the lifetime health advisory for PFOA and PFOS of 70 ng/L apply to both short-term (i.e. weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios. EPA also recommended that when PFOA and PFOS co-occur at the same time and location in a drinking water source, a conservative and health-protective approach would be to compare the sum of the concentrations (PFOA + PFOS) to the 70 ng/L health advisory. This recommendation was based on the observation that adverse effects observed following exposures to PFOA and PFOS are the same or similar and the reference doses for both PFOA and PFOS are based on similar developmental effects and are numerically identical.

Following this logic set forth by the EPA, PFNA is also being included in the 70 ng/L translation level for PFOA and PFOS (Table 3). The Agency for Toxic Substances and Disease Registry (ATSDR) drafted toxicity values, referred to as minimal risk levels, for four PFAS (PFOA, PFOS, PFHxS and PFNA). The minimal risk level drafted for PFOA, PFOS, and PFNA were $3x10^{-6}$, $2x10^{-6}$, and $3x10^{-6}$ mg/kg/day, respectively. The minimal risk levels for these three PFAS were based on developmental effects observed in animal toxicity studies.[10] Thus, because PFNA exhibits the same order of magnitude level of toxicity as PFOA and PFOS and because the critical effect for PFNA is also developmental toxicity, a conservative and health-protective approach to compare the sum of the concentrations (PFOA + PFOS + PFNA + any identified parents) to the translation level of 70 ng/L will be used.

A translation level of 700 ng/L was selected for PFHxS (Table 3). The minimal risk level drafted by ATSDR for PFHxS was $2x10^{-5}$, which is an order of magnitude greater than the minimal risk levels for PFOA, PFOS, and PFNA, and is based on observed endocrine effects in the critical study performed in rats. The critical effect observed for PFHxS was not the same as for PFOA, PFOS, and PFNA; thus, concentrations of PFHxS will only be combined with the adjusted concentrations of any identified parents, prior to comparing to the translation level. At the drafting of this policy, no parent constituents for PFHxS have been identified from the monitoring list shown in Table 1. The translation level for PFHxS was set at an order of magnitude greater than the translation level set for PFOA, PFOS, and PFNA to reflect the relative difference in toxicity observed between PFHxS compared to PFOA, PFOS, and PFNA.

A translation level of 400,000 ng/L was selected for PFBS (Table 3). The translation level for PFBS was based on an EPA Regional Screening Level in tap water derived from EPA's Provisional Peer-Reviewed Toxicity Values. The critical effect observed for PFBS was renal

[7] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf
[8] https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final_508.pdf
[9] https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf
[10] https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf (Tables 1-3, 1-4, and 1-6)

toxicity.[11] Thus, concentrations of PFBS will only be combined with the adjusted concentrations of any identified parent constituents, prior to comparing to the translation level. At the drafting of this policy, no parent constituents for PFBS have been identified from the monitoring list shown in Table 1. The commission recommends that these translation levels be reviewed by 2025. In addition, the commission recognizes that the division retains the authority to implement more stringent translation values for PFOA, PFOS, PFNA, PFHxS, and PFBS or translation levels for other PFAS constituents pursuant to the narrative standard where scientifically supportable (for example where additional toxicological data or site-specific information become available). The commission encourages the division to include appropriate stakeholder engagement commensurate with the scope of deviation from this Policy as well as updates to the Policy for transparency where applicable.

Table 3 Translation Levels for PFOA, PFOS, PFNA, PFHxS, and PFBS

PFAS	Translation Level (ng/L)
PFOA	70*
PFOA parent constituents: 8:2 FTS (adjusted)**	
PFOS	
PFOS parent constituents: NEtFOSAA, NMeFOSAA, and PFOSA/FOSA (adjusted)**	
PFNA	
PFHxS	700
PFBS	400,000

*Individually or combined

**See Table 2, fifth column for adjustment. Examples: Example 1 - 8:2 FTS, PFOS, and PFOA were measured in a system at 30 ng/L, 20 ng/L, and 50 ng/L, respectively. (30 ng/L * 0.78) + 20 ng/L + 50 ng/L = 93.4 ng/L. This would exceed the translation level of 70 ng/L. Example 2 - In a separate sampling event or system, if 20 ng/L of PFNA and 55 ng/L of PFOSA were measured, this would exceed the translation level: 20 + (55 * 1) = 75 ng/L. Example 3 - In a separate sampling event or system, NEtFOSAA and NMeFOSAA were measured at 45 and 30 ng/L respectively, this would not exceed the translation level: (45 * 0.85) + (30 * 0.88) = 65 ng/L.

VIII. Cleanup of PFAS Contaminated Groundwater

The HMWMD implements the commission's numeric and narrative groundwater standards through its hazardous waste, radiation, remediation, and solid waste and materials management programs. The purpose of this section is to clarify how the HMWMD is currently addressing PFOA and PFOS through its hazardous waste program and how the narrative standards could potentially be considered in Comprehensive Environmental Response,

[11] https://cfpub.epa.gov/ncea/pprtv/documents/PotassiumPerfluorobutaneSulfonate.pdf

Compensation, and Liability Act (CERCLA) remedial efforts in the future. This narrative policy does not establish a PFAS cleanup policy for HMWMD.

HMWMD focuses on facilities that dispose of or cleanup hazardous waste under a hazardous waste land disposal permit or a compliance order, pursuant to the Resource Conservation and Recovery Act (RCRA). Under the Colorado Hazardous Waste Regulations, 6 CCR 1007-2, Part 261, Appendix VIII, PFOA and PFOS were added as hazardous constituents by the Solid and Hazardous Waste Commission. As a result of the hazardous constituent listings, the HMWMD can require that any releases of PFOA or PFOS at a facility under a hazardous waste permit or order be investigated, cleaned-up, or otherwise remediated as necessary to ensure the protection of human health and the environment regardless of when the releases may have occurred. This policy aligns the Water Quality Control Division and the HMWMD for considering PFOA and PFOS statewide. Specifically, control of PFAS discharges from point sources will now be considered along with cleanup of PFOA and PFOS at RCRA sites.

HMWMD also focuses on the remediation of properties with media contaminated with hazardous substances under the CERCLA. For remediation to be complete under CERCLA, the site must achieve the remedial action objectives and comply with all ARARs. The narrative standards in Regulations No. 31.11(1)(a)(iv) and No. 41.5(A)(1) will be considered ARARs for sites where the remedy is required to address drinking water or groundwater. This policy will not be used to measure whether the remediation is complete; however, the policy may be considered for implementing the narrative standards. On the remedial decision document this would be referred to as "to be considered" if the narrative standards are ARARs.

In addition to RCRA and CERCLA efforts, C.R.S. 25-8-606 gives the Water Quality Control Division the authority to issue cleanup orders. C.R.S. 25-8-606 states that the Water Quality Control Division may issue orders to any person to cleanup any material which they, their employee, or their agent has accidentally or purposely dumped, spilled, or otherwise deposited in or near state waters which may pollute them. The Water Quality Control Division has used this provision rarely for groundwater cleanup. The HMWMD is generally the entity in the department responsible for cleanup of hazardous materials and solid waste.

IX. Implementation in the Colorado Discharge Permit System

The division issues permits to dischargers of pollutants to state surface and groundwater under the Colorado Discharge Permit System . With regard to groundwater, the division only issues permits when the activities are not under the jurisdiction of the groundwater implementing state agencies.

The division should consider this policy in Colorado Discharge Permit System permits in a number of ways, including the following:

1. Monitoring in permits and through the permits' duty to provide information clause when requested.
2. Continued monitoring and source investigations.
3. Monitoring, source investigations and effluent limits.

Monitoring

The commission's expectation is that the division may require monitoring through permit application requirements, through specific permit terms or through a permit's existing duty to provide information provision. This standard permit provision states that a permittee "shall furnish to the division any information which the division may request to determine whether cause exists for modifying or revoking and reissuing the permit, or to determine compliance with the permit." The division may also add some or all of the PFAS listed in this policy's Table 1 to its standard list of "Toxic Pollutants and Hazardous Substances Required To Be Identified by Existing Dischargers if Expected To Be Present" which are included in the division's permits.

Initial monitoring should be focused on facilities with a likelihood of PFAS discharges to state waters (ground or surface waters). This would be done using information from surveys sent to firefighting districts, future discharger surveys initiated by the division, duty to provide monitoring data, locations near known or potential sources, collection systems containing likely or known sources, and facility type.

When included in permits, the frequency of monitoring should be consistent with the division's existing baseline monitoring frequency policy, Water Quality Permit-20. Under this policy, the permit writer will take into account the type of activity producing the discharge, the size of the discharge, and the variability of the discharge when determining monitoring frequency. In addition, the policy states that when an entity demonstrates that laboratory facilities are not available to run a required test, where results cannot be obtained at the required frequency due to physical constraints, or where the entity demonstrates that extreme economic hardship would result from compliance with this policy, the division may substitute an alternative monitoring frequency requirement.

Continued Monitoring and Source Investigation

Once the division has PFAS monitoring data for a facility, it should evaluate those data and consider whether further action is needed. PFAS are manmade, so there is no natural background level for these constituents. Therefore, when monitoring shows that a specific PFAS is present at or above the reporting levels in Table 1 of this policy, the division may take action, including requiring continued monitoring and source investigations. Continued

monitoring may also be required if a permitted facility is otherwise at risk for future PFAS discharges (for instance, if a groundwater dewatering outfall is adjacent to a known source of PFAS). Source investigations could include identifying potential sources, evaluating source control options, industrial user inventories, or other investigations. Source investigations are likely to be required at municipal wastewater facilities with pretreatment programs and at large industrial facilities. With regards to construction dewatering and other simple groundwater dewatering operations, source investigations shall not be required of the permittee unless the permittee is reasonably expected to be the source of the PFAS contamination.

Effluent Limits

The division should establish numeric effluent limits based on the commission's translation of the narrative standards in Table 3 of this policy. Effluent limits should be further based on analyses of reasonable potential consistent with Clean Water-1 (the division's existing Reasonable Potential policy) or the specific reasonable potential procedures identified in the relevant general permit. However, the division also has, under this policy, the discretion to apply report-only monitoring or practice-based controls requirements, rather than numeric effluent limits, when there is a lack of data or there is significant uncertainty associated with a discharge, like short-term discharges of uncertain quantity. The division also has the discretion to postpone effluent limits for domestic wastewater facilities for the first permit term in order to give those facilities the opportunity to monitor and, if needed, to develop robust source control programs. The division should not apply the provisions of Regulation No. 31.8 (the antidegradation rule) or the division's antidegradation guidance in the determination of criteria to implement the narrative standards with respect to PFAS.

Based on the information contained in the EPA health advisory, the levels set for PFOA and PFOS are protective of both short-term and chronic exposure scenarios. Application of the levels as protective of short-term exposures is appropriate because of the determination of the critical effect being developmental toxicity. As such, the translation values shown in Table 3 for PFOA, PFOS, PFNA, and their parent constituents (PFAS for which the critical effect of developmental toxicity has been used to derive the translation level) should be applied as both 30-day average and daily maximum effluent limits. The remaining PFAS for which translation levels have been set (PFHxS and PFBS) should be applied only as 30-day average effluent limits.

For purposes of assessing ambient water quality in Colorado, non-detects are typically treated as "zeros". This approach should also be followed for calculating effluent limits for PFAS, where applicable. Reporting PFAS effluent data below detection should follow the Division's Discharge Monitoring Report Guidance.

The division should also, of course, establish practice-based effluent limits for PFAS when appropriate. With regards to stormwater, limits or use conditions will apply only to those permittees using or possessing materials containing PFAS. Given the ubiquitous nature of PFAS, it is not the commission's intent that this policy be used to require numeric effluent limits for PFAS in stormwater discharges.

Finally, while the commission recommends that the division establish numeric effluent limits based on the commission's translation of the narrative standards in Table 3 of this policy, the division of course retains the authority to implement more stringent translation values under its authority and responsibility to implement the narrative standard where scientifically supportable (for example where additional toxicological data or site-specific information become available).

Scope of Application

Monitoring, source investigation, and effluent limits for PFAS would be implemented for the protection of surface water and groundwater used for drinking water or with the ability to affect drinking water. As such, the commission believes it would be appropriate to apply these tools: for discharges to surface water classified as Water Supply; to protect a downstream water classified as Water Supply; groundwater areas where the department must protect all potential uses (i.e., the areas protected by the "interim narrative standard" in Regulation No. 41.5(C)(6)(b)(i)(B)); and specified groundwater areas with water classified for domestic uses.

The last of these includes Specified Area 7 (City of Fountain, Security Water District, Stratmoor Hills Water District, and Widefield Water and Sanitation District wellfields, El Paso County), as described in the commission's Regulation No. 42.7(7). The commission has already established groundwater standards for PFOA and PFOS in Specified Area 7. However, those standards do not have the same role or purpose as the narrative standard, which is broader and more stringent, requiring that groundwater shall be free from all pollutants that alone or in combination with other substances are toxic to human beings (Reg. No. 41.5(A)(1)). The commission encourages the division to apply this policy to Specified Area 7 as well as the commission's site-specific PFOA and PFOS standards in order to ensure that both the narrative standard and the site-specific standards are met in Specified Area 7. The commission understands that applying both the site-specific and narrative standards to this area may result in effluent limits for PFOA and PFOS that are less than 70 ng/L. This is appropriate, as such effluent limits must ensure that there will not be exceedances of any standard, whether it be a site-specific standard or a narrative standard. See Reg. No. 61.8(1)(e) (barring the division from issuing a permit which allows a discharge that will result in pollution of the receiving waters in excess of the applicable water quality standards except by using a compliance schedule or variance).

Application to Colorado's Implementation of Section 401 of the Clean Water Act to EPA Section 402 Permits

Pursuant to Section 401 of the federal Clean Water Act, EPA issuance of federal Clean Water Act Section 402 discharge permits issued for federal facilities require a certification from Colorado where the authorization of the activity will not result in a violation of water quality standards. The 401 certification constitutes the state's finding that there is a reasonable assurance that the activity will be conducted in a manner which will not violate applicable water quality standards. 33 U.S.C. § 1341(a)(1); 40 C.F.R. § 121.2(a)(3); Chostner v. Colorado Water Quality Control Commission, 327 P.3d 290, 2013 COA 111 (2013). Under the commission's Regulation No. 82, the division may approve, conditionally approve, or deny Section 401 certification requests. Denial of certification triggers denial of the EPA permit.

The division is strongly encouraged to use its authority under Section 401 and Regulation No. 82 to help ensure that federal discharge permits contain PFAS monitoring requirements, source investigation conditions, effluent limits, or other terms and conditions like those described in Section IX for Colorado Permit Discharge System permits so that federal activities and discharges to state waters are conducted in a manner which will not violate Colorado's narrative water quality standards.

X. Applicability to Colorado's List of Impaired Waters

Consistent with the commission's biennial review and adoption of Colorado's List of Impaired Waters, information may be submitted as part of the Regulation No. 93 rulemaking hearing if any entity wishes to propose surface waters impaired for a particular PFAS. The rulemaking hearings for Regulation No. 93 are typically scheduled for early winter in the odd numbered years (2021, 2023 etc). PFAS data and Policy 20-1 may be considered in assessment efforts as part of this rulemaking hearing. No separate rulemaking hearing is necessary. Colorado's List of Impaired Waters does not include groundwater.

Narrative standards describe conditions that, if exceeded, result in unacceptable water quality conditions. Narrative standards that are applied to all surface waters in Colorado address sediment, floatables, film, odor, taste, color, toxins and excessive nutrients. Exceedance of narrative standards is more difficult to ascertain, as there are typically no quantifiable expressions of parameter concentration or loading that result in nonattainment.

Attainment of the translation levels in this policy may serve as a surrogate measure indicating attainment of the narrative standards. The 303(d) Listing Methodology has historically allowed for information and surrogate measures to be used in listing decisions if an entity brings supporting information and data forward.

Proposals for the 303(d) List of impaired waters, including listings based on the narrative standard, must be:

- Timely and compliant with the rulemaking hearing process deadlines
- Based on existing and readily available data
- Based on credible and representative data
- For surface waters (The Colorado 303(d) List does not consider groundwater listings)

XI. Consideration of Economic Reasonableness Under Section 25-8-102(5), C.R.S.

As part of the legislative declaration of the Water Quality Control Act (WQCA), Section 25-8-102(5), C.R.S. requires that consideration be given to the economic reasonableness of any final action (except enforcement actions) before the action is taken. Such consideration shall include evaluation of the benefits derived from achieving the goals of the WQCA and the economic, environmental, public health, and energy impacts to the public and affected persons of the action. Some of these considerations are summarized below.

Benefits of the policy

The policy will allow the department, particularly the division, to better understand and potentially limit, when appropriate, discharges of PFAS into state waters serving as water supplies for Coloradans in order to protect those waters for domestic uses.

There is frequently a direct connection between the effluent permitted facilities under the Colorado Discharge Permit System put into state waters and what is taken out for drinking water. For instance, many Coloradans receive their drinking water directly from state surface waters or from alluvial wells that are directly influenced by surface waters. Surface waters used in this way as a source for drinking water are assigned the use of "Water Supply" by the commission. As of February 2020, the commission has designated 806 segments (of 1,051 statewide) with the Water Supply use. Thousands of facilities have Colorado Discharge Permit System permits to discharge directly to (or upstream of) Water Supply segments. These include large wastewater treatment plants that discharge millions of gallons a day of effluent directly upstream of the intakes for large drinking water systems. Examples of this include:

- Metro Wastewater Reclamation District discharges its effluent directly upstream of drinking water intakes for the City of Thornton, Todd Creek Village, and Aurora Water's Binney Water Purification Facility. The Aurora Water facility supplies both

Aurora residents and the Water, Infrastructure and Supply Efficiency (WISE) regional partnership system.

- Centennial Water and Sanitation District discharges directly upstream of the City of Englewood's drinking water intake.
- Plum Creek Water Reclamation Authority wastewater discharge supplements the raw water used by Castle Rock's drinking water system, Castle Rock Water.
- Winter Park and Fraser's wastewater treatment plants are directly upstream of the Town of Granby's drinking water intake.
- Idaho Springs and Georgetown wastewater treatment plants discharge to Clear Creek above an intake for the City of Blackhawk's drinking water system.

The division also permits more than a hundred facilities that discharge effluent to groundwater within one half a mile of a drinking water well. Other facilities discharge effluent into confined groundwater aquifers with many drinking water wells. For example, Cherokee Metro District discharges wastewater to the Upper Black Squirrel Aquifer, a designated basin used for drinking water through private wells by many homes in the area.

As discussed, one of the first steps the division will take under the policy is to expand monitoring for PFAS in discharges to state waters. This information will be publicly available and will allow those using water downstream of dischargers or in close proximity to discharges to be better aware of these PFAS discharges. Monitoring information will also allow the department as a whole to better understand the prevalence of and potential exposures to PFAS throughout the state. Gaining this better understanding of PFAS discharges is a significant benefit of this policy as there is limited information available as of mid-2020. This better understanding will help the commission determine appropriate future steps to address this important contamination issue.

Limiting discharges of PFAS into state waters used as water supply through source investigation, source control, and effluent limits when appropriate will further benefit the state. Limiting PFAS in these ways to state waters used as water supply will decrease the risk of drinking PFAS-contaminated water to those Coloradans who receive water from drinking water intakes downstream of permitted discharges, from alluvial wells downstream of permitted dischargers, and from groundwater wells that are close to permitted dischargers. It will not eliminate the risk of drinking PFAS-contaminated water for Coloradans altogether. As noted, groundwater contamination may already be present and other sources of PFAS may exist, but limiting PFAS discharges will decrease these risks.

Decreasing the risk of drinking PFAS-contaminated water to those Coloradans who receive water from drinking water intakes downstream of permitted discharges, from alluvial wells downstream of permitted dischargers, and from groundwater wells that are close to permitted dischargers will save Coloradans many costs. Expenses associated with PFAS-

contaminated drinking water can include: the costs of illness; lost wages due to illness; the costs of providing a temporary uncontaminated drinking water supply; and the costs of treating PFAS- contaminated water.[12] There may also be economic damage to businesses and property values in communities whose water has been contaminated.

These are significant economic costs, and avoiding them will be an economic benefit. For instance, treating PFAS can be expensive for drinking water systems and homeowners. Cost information from drinking water design applications submitted by water providers impacted by Peterson Air Force Base estimate the capital cost of PFAS treatment (consisting of ion exchange with redundancy) at $94,000 for 50 gallons per minute treatment capacity and $2,500,000 for 1,200 gallons per minute treatment capacity. Operating costs for these treatment systems may go on in perpetuity. While there may be lower cost options of addressing PFAS contamination, in some cases treatment may be the only option. Providing temporary uncontaminated supplies also has both economic and environmental costs. In addition to the costs of hauling and buying the uncontaminated water, when groundwater becomes contaminated with high levels of PFAS, public water systems in Colorado have increased their reliance upon Colorado's stretched surface waters. Lowering the risk of having communities switch their water supply from groundwater to surface water is an additional and significant benefit. The costs of illness are also likely high, albeit complicated to measure. The Centers for Disease Control considers the costs of illness to include: medical costs, such as the cost of diagnostic tests, physician office visits, and drugs and medical supplies; non-medical costs, such as travel costs for obtaining care and related childcare costs; and productivity losses for patients and caregivers.[13]

There are significant public health benefits to decreasing the risk of drinking PFAS-contaminated water to those Coloradans who receive water from drinking water intakes downstream of permitted discharges, from alluvial wells downstream of permitted dischargers, and from groundwater wells that are close to permitted dischargers. PFAS has been linked to increased cholesterol levels, liver damage or changes in liver function, decreases in how well the body responds to vaccines, increases in the risk of an asthma diagnosis, increases in the risk of thyroid disease, decreases in fertility in women, and increases in the risk of serious conditions like high blood pressure or pre-eclampsia in pregnant women.[14] People exposed to high levels may have increased risk of certain cancers.

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[12] Gretta Goldenman, Meena Fernandes, Michael Holland, Tugce Tugran, Amanda Nordin, Cindy Schoumacher and Alicia McNeill, The cost of inaction, A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS (2019), THE COST OF INACTION (last viewed Feb. 27, 2020).

[13] Centers for Disease Control, Office of the Associate Director for Policy and Strategy, Costs of Illness, https://www.cdc.gov/policy/polaris/economics/cost-of-illness.html (last viewed Feb. 27, 2020).

[14] [ATSDR] Agency for Toxic Substances and Disease Registry. 2018. Toxicological profile for Perfluoroalkyls. (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. [updated 2018 June; accessed 2019 August 21] Available from: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237

However, these studies are not consistent and may not have looked at other factors like smoking.[14] The International Agency for Research on Cancer investigated PFOA and found limited evidence in human and animal studies that linked PFOA to cancer. They classified PFOA as possibly causing cancer (placed in Group 2B) especially with testicular and kidney cancers.[14,15] Neither the International Agency for Research on Cancer nor the Department of Health and Human Services have evaluated if other PFAS can cause cancer. The EPA suggests that there is evidence that PFAS may have the potential to cause cancer.[14]

Probable links between exposure to certain PFAS and health effects in humans have been previously noted, including what is described in the C8 Science Panel publications.[16] For two PFAS for which the policy includes translation levels, PFOA and PFOS, both animal toxicity and human epidemiological evidence support quantitative risk assessment.[17,18] For the additional PFAS for which translation levels have been included in the policy (PFHxS, PFBS, and PFNA), evidence for animal toxicity exists as well as human epidemiological evidence suggesting that these compounds may have similar effects in humans.[19,20] ATSDR, EPA, and other states have performed systematic reviews of published research and found the data sufficient for setting forth health-based levels for not only PFOA and PFOS, but also other PFAS. Health effects of PFAS are the current focus of much research, including several studies here in Colorado. As new studies become available, our understanding of the health effects of these compounds in humans will continue to grow. Decreasing exposure to PFAS in Colorado communities may reduce these potential health effects and associated costs to address them.

There are also environmental benefits to limiting and preventing discharges of PFAS to state waters. PFAS have been ubiquitously found in aqueous and terrestrial environments around the world. They have been detected in zooplankton, invertebrates, reptiles, fish, birds, and mammals. PFOS is the most commonly detected PFAS and has a higher potential to biomagnify compared to other studied PFAS. This may impact humans like recreational and subsistence fishermen who consume more fish in their diet. Additionally, data on PFAS toxicity to aquatic organisms is growing.

Economic, environmental, public health, and energy impacts of the policy

[15] [IARC] International Agency for Research on Cancer. 2017. IARC monograph 110 Perfluorooctanoic acid. Lyons, France: International Agency for Research on Cancer. [accessed 2019 August 21] Available from: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono110-01.pdf
[16] http://www.c8sciencepanel.org/index.html
[17] https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf
[18] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf
[19] https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf
[20] https://www.epa.gov/sites/production/files/2018-11/documents/pfbs_public_comment_draft_toxicity_assessment_nov2018-508.pdf

Monitoring and Source Investigations. The economic impacts of the policy will include increased monitoring costs for some dischargers. PFAS monitoring is more expensive than monitoring for many other constituents. At this time, the average cost per sample is about $300 and may be as high as $400. Source investigations may use dischargers' time and staff resources. The investigations may result in additional costs associated with changing current PFAS use or disposal practices for those discharging to wastewater treatment plants or for industrial dischargers.

Effluent Limits. As discussed previously, the department plans to require monitoring, not effluent limits, for the majority of domestic wastewater facilities for the first permit term in order to evaluate the data and determine whether grounds exist under the Reasonable Potential policy to require effluent limits. In addition, the proposed policy provides the division with the flexibility to apply report-only monitoring requirements or practice-based controls rather than numeric effluent limits when there is a lack of data or there is significant uncertainty associated with a discharge. The division will also use its permitting tools, like compliance schedules, to allow existing dischargers the time necessary to achieve compliance. Such schedules will in part depend upon the costs and feasibility of coming into compliance with those limits. Other tools available to the regulated community when other regulatory tools have been exhausted include discharger specific variances in front of the commission and (for groundwater) permit variances under Regulation 61.12.

If and when effluent limits are effective, treatment will not necessarily be required. Source control has been shown to lower PFAS levels significantly in other states, particularly Michigan, and may be sufficient to meet those limits. Source control may use dischargers' time and staff resources. They may also result in additional costs associated with changing current PFAS use or disposal practices for those discharging to wastewater treatment plants or for industrial dischargers.

If treatment is required, the treatment technology and scale would be driven by a number of factors, including:

- What are the specific PFAS present in the influent and at what concentration?
- What is the current type of treatment and how much does the current treatment incidentally remove PFAS?
- What is the land footprint available at the treatment facility for constructing additional treatment?
- What are the options for disposal of waste products?
- What is the effluent limitation and is it applied as an acute or chronic limitation?
- What are other pollutants that may compete with existing treatments and typical PFAS treatments?

At this time, PFAS treatment technologies typically involve Reverse Osmosis (RO), Granular Activated Carbon (GAC) or Anion Exchange. Most (but not all) current treatment technologies work better when preceded by turbidity treatment. Numerous options for such turbidity treatment exist, including fairly affordable options with small footprints, like cloth disc filters and an upflow sand filter (continuous flow). Capital costs for these systems may range from several thousands dollars to several million or more depending on the size of the system. In addition, these turbidity treatment facilities may also require new land that may or may not be available at the required, or desired, locations. New PFAS treatment technologies, including some with more streamlined treatment, are rapidly developing, but testing and confirming their efficacy and applicability will take time. Some of these new technologies may be available when effluent limits become effective in the future.

PFAS treatment systems will also require additional expenditures for operations and maintenance and waste disposal. These costs could be, depending on the size of the plant, thousands to hundreds of thousands of dollars a year, if not more. For instance, GAC systems need their carbon filters replaced periodically. Some PFAS treatment technologies generate PFAS waste streams that need to be brought to an authorized disposal site, which can be costly.

The installation of wastewater treatment technologies may also have energy impacts. Many of these treatment technologies, like reverse osmosis, are relatively energy intensive. Pumping water for treatment may also use energy. In addition, if PFAS waste is incinerated, significant energy may be required to incinerate all the PFAS wastes. And trucking PFAS effluent and/or treatment wastes, particularly trucking it out of states, will use significant quantities of gasoline. Gaining a better understanding of the incremental increased energy usage associated with potential PFAS treatment to the current energy usage at treatment facilities will be helpful moving forward.

Economic impacts from effluent limits (including practice-based limits) besides treatment costs could include: having to adjust industrial practices to phase out materials containing high levels of PFAS; construction delays; securing, properly storing, and properly disposing of PFAS-containing materials; and hauling waste rather than disposing of it in state waters. And to the extent that this policy makes cleanup and treatment of contaminated groundwater more likely, the parties responsible for that cleanup may incur additional costs.

Not all of these costs will have to be borne by the dischargers, particularly by publicly owned domestic treatment plants. The department has a number of grant and loan programs to offset some of those costs and is seeking additional ways to offer financial assistance to facilities to address PFAS. Potential funding sources for improvements to wastewater treatment facilities include State Revolving Fund (SRF) loans, Water Quality Improvement Fund (WQIF) grants, and Small Community Grants (SCG). There are different criteria for each

of these programs that the facility owners need to meet in order to be eligible.[21] USDA and Department of Local Affairs (DOLA) grants or loans may also be available. In addition, a 2020 law, SB20-218, establishes a perfluoroalkyl and polyfluoroalkyl substances cash fund to be used for, among other purposes, water system infrastructure used for the treatment of identified PFAS.[22] SB20-218 also establishes a takeback program for materials containing PFAS that may help facilities properly dispose of existing materials onsite that contain PFAS. Finally, EPA has committed to providing data, tools and guidance to operators on management of PFAS in wastewater, biosolids, wastewater reuse, and pretreatment.[23]

The commission does not anticipate that this policy will have significant adverse environmental and public health impacts. Rather, as noted above, it is expected to have environmental and public health benefits.

XII. Routine Review of Policy

The routine review of this policy will be consistent with the commission's routine review of all of the commission's regulations and policies. The commission will review the progress that has been achieved through this policy in 2025, unless the commission determines that a review of the policy is needed sooner or the division requests an update prior to that if new translation levels are scientifically supportable. At that time, the commission will consider whether continuation of this policy is appropriate, or whether it should be deleted or modified based on the circumstances that exist at a state and national level at that time.

XIII. Policy Determinations

A. July 14, 2020 Adoption of Policy 20-1

The commission intends to include a statement of its policy determinations for adoption of this policy in the meeting summary for its July 13-14, 2020 meeting.

[21] See https://www.colorado.gov/pacific/cdphe/SRF-info and https://www.colorado.gov/pacific/cdphe/wq-grants
[22] http://leg.colorado.gov/bills/sb20-218
[23] https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=537694&Lab=NRMRL

Exhibit 87

United States
Environmental Protection
Agency

Office of Water
Office of Science and Technology
4304

EPA-822-B-00-004
October 2000

Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)

2020 TR LANL-01853

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Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)

Final

Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, DC 20460

2020 TR LANL-01854

NOTICE

The policies and procedures set forth in this document are intended solely to describe EPA methods for developing or revising ambient water quality criteria to protect human health, pursuant to Section 304(a) of the Clean Water Act, and to serve as guidance to States and authorized Tribes for developing their own water quality criteria. This guidance does not substitute for the Clean Water Act or EPA's regulations; nor is it a regulation itself. Thus, it does not impose legally-binding requirements on EPA, States, Tribes or the regulated community, and may not apply to a particular situation based upon the circumstances.

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

2020 TR LANL-01855

FOREWORD

This document presents EPA's recommended Methodology for developing ambient water quality criteria as required under Section 304(a) of the Clean Water Act (CWA). The Methodology is guidance for scientific human health assessments used by EPA to develop, publish, and from time to time revise, recommended criteria for water quality accurately reflecting the latest scientific knowledge. The recommended criteria serve States and Tribes' needs in their development of water quality standards under Section 303(c) of the CWA.

The term "water quality criteria" is used in two sections of the Clean Water Act, Section 304(a)(1) and Section 303(c)(2). The term has a different program impact in each section. In Section 304, the term represents a scientific assessment of ecological and human health effects that EPA recommends to States and authorized Tribes for establishing water quality standards that ultimately provide a basis for controlling discharges or releases of pollutants. Ambient water quality criteria associated with specific stream uses when adopted as State or Tribal water quality standards under Section 303 define the maximum levels of a pollutant necessary to protect designated uses in ambient waters. The water quality criteria adopted in the State or Tribal water quality standards could have the same numerical limits as the criteria developed under Section 304. However, in many situations States and authorized Tribes may want to adjust water quality criteria developed under Section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. When adopting their water quality criteria, States and authorized Tribes have four options: (1) adopt EPA's 304(a) recommendations; (2) adopt 304(a) criteria modified to reflect site-specific conditions; (3) develop criteria based on other scientifically defensible methods; or (4) establish narrative criteria where numeric criteria cannot be determined.

EPA will use this Methodology to develop new ambient water quality criteria and to revise existing recommended water quality criteria. It also provides States and authorized Tribes the necessary guidance to adjust water quality criteria developed under Section 304 to reflect local conditions or to develop their own water quality criteria using scientifically defensible methods consistent with this Methodology. EPA encourages States and authorized Tribes to use this Methodology to develop or revise water quality criteria to appropriately reflect local conditions. EPA believes that ambient water quality criteria inherently require several risk management decisions that are, in many cases, better made at the State, Tribal, or regional level. Additional guidance to assist States and authorized Tribes in the modification of criteria based on the Methodology will accompany this document in the form of three companion Technical Support Documents on Risk Assessment, Exposure Assessment, and Bioaccumulation Assessment.

_____

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Potential areas for conflict of interest were investigated via direct inquiry with the peer reviews and review of their current affiliations. No conflicts of interest were identified.

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LIST OF ACRONYMS

ADI	Acceptable Daily Intake
ARAR	Applicable or Relevant and Appropriate Requirements
ASTM	American Society of Testing and Materials
AWQC	Ambient Water Quality Criteria
BAF	Bioaccumulation Factor
BAF_{ℓ}^{fd}	Baseline Bioaccumulation Factor
BCF	Bioconcentration Factor
BCF_{ℓ}^{fd}	Baseline Bioconcentration Factor
BCF_{T}^{t}	Bioconcentration Factor Based on Total Concentrations in Tissue and Water
BMD	Benchmark Dose
BMDL	Lower-Bound Confidence Limit on the BMD
BMF	Biomagnification Factor
BMR	Benchmark Response
BSAF	Biota-Sediment Accumulation Factors
BW	Body Weight
C_{ℓ}	Lipid-normalized Concentration
C_{soc}	Organic Carbon-normalized Concentration
C_t	Concentration of the Chemical in the Specified Wet Tissue
C_w	Concentration of the Chemical in Water
CDC	U.S. Centers for Disease Control and Prevention
CSFII	Continuing Survey of Food Intake by Individuals
CWA	Clean Water Act
DDT	1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
DDE	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
DDD	1,1-dichloro-2,2-bis(p-chlorophenyl)ethane
DI	Drinking Water Intake
DNA	Deoxyribonucleic Acid
DNOC	2,4-dinitro-o-cresol
DOC	Dissolved Organic Carbon
ED_{10}	Dose Associated with a 10 Percent Extra Risk
EPA	Environmental Protection Agency
f_{fd}	Fraction Freely Dissolved
f_{ℓ}	Fraction Lipid
FCM	Food Chain Multiplier
FEL	Frank Effect Level
FI	Fish Intake
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GLI	Great Lakes Water Quality Initiative
HCBD	Hexachlorobutadiene
IARC	International Agency for Research on Cancer
II	Incidental Ingestion
ILSI	International Life Sciences Institute

IRIS	Integration Risk Information System
kg	kilogram
K_{ow}	Octanol-Water Partition Coefficient
L	Liter
LAS	Linear Alkylbenzesulfonate
LED_{10}	The Lower 95 Percent Confidence Limit on a Dose Associated with a 10 Percent Extra Risk
LMS	Linear Multistage Model
LOAEL	Lowest Observed Adverse Effect Level
M_l	Mass of Lipid in Specified Tissue
M_t	Mass of Specified Tissue (Wet Weight)
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MF	Modifying Factor
mg	Milligrams
ml	Milliliters
MOA	Mode of Action
MOE	Margin of Exposure
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NFCS	Nationwide Food Consumption Survey
NHANES	National Health and Nutrition Examination Survey
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NPDES	National Pollutant Discharge Elimination System
PAH	Polycyclic Aromatic Hydrocarbon
PCB	Polychlorinated Biphenyls
POD	Point of Departure
POC	Particulate Organic Carbon
RDA	Recommended Daily Allowance
RfC	Reference Concentration
RfD	Reference Dose
RfD_{DT}	Reference Dose for Developmental Effects
RPF	Relative Potency Factor
RSC	Relative Source Contribution
RSD	Risk-Specific Dose
SAB	Science Advisory Board
SDWA	Safe Drinking Water Act
SF	Safety Factor
STORET	Storage Retrieval
TEAM	Total Exposure Assessment Methodology
TEF	Toxicity Equivalency Factor
TMDL	Total Maximum Daily Load
TSD	Technical Support Document
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency

UF	Uncertainty Factor
WQBEL	Water Quality-Based Effluent Limits

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1. INTRODUCTION

1.1 WATER QUALITY CRITERIA AND STANDARDS

Pursuant to Section 304(a)(1) of the Clean Water Act (CWA), the U.S. Environmental Protection Agency (EPA) is required to publish, and from time to time thereafter revise, criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on human health which may be expected from the presence of pollutants in any body of water.

Historically, the ambient water quality criteria (AWQC or 304(a) criteria) provided two essential types of information: (1) discussions of available scientific data on the effects of the pollutants on public health and welfare, aquatic life, and recreation; and (2) quantitative concentrations or qualitative assessments of the levels of pollutants in water which, if not exceeded, will generally ensure adequate water quality for a specified water use. Water quality criteria developed under Section 304(a) are based solely on data and scientific judgments on the relationship between pollutant concentrations and environmental and human health effects. The 304(a) criteria do not reflect consideration of economic impacts or the technological feasibility of meeting the criteria in ambient water. These 304(a) criteria may be used as guidance by States and authorized Tribes to establish water quality standards, which ultimately provide a basis for controlling discharges or releases of pollutants into ambient waters.

In 1980, AWQC were derived for 64 pollutants using guidelines developed by the Agency for calculating the impact of waterborne pollutants on aquatic organisms and on human health. Those guidelines consisted of systematic procedures for assessing valid and appropriate data concerning a pollutant's acute and chronic adverse effects on aquatic organisms, nonhuman mammals, and humans.

1.2 PURPOSE OF THIS DOCUMENT

The *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)* (hereafter the "2000 Human Health Methodology") addresses the development of AWQC to protect human health. The Agency intends to use the 2000 Human Health Methodology both to develop new AWQC for additional pollutants and to revise existing AWQC. Within the next several years, EPA intends to focus on deriving AWQC for chemicals of high priority (including, but not limited to, mercury, arsenic, PCBs, and dioxin). Furthermore, EPA anticipates that 304(a) criteria development in the future will be for bioaccumulative chemicals and pollutants considered highest priority by the Agency. The 2000 Human Health Methodology is also intended to provide States and authorized Tribes flexibility in establishing water quality standards by providing scientifically valid options for developing their own water quality criteria that consider local conditions. States and authorized Tribes are strongly encouraged to use this Methodology to derive their own AWQC. However, the 2000 Human Health Methodology also defines the default factors EPA intends to use in evaluating and determining consistency of State water quality standards with the requirements of the CWA. The Agency intends to use these default factors to calculate national water quality criteria under

Section 304(a) of the Act. EPA will also use this Methodology as guidance when promulgating water quality standards for a State or Tribe under Section 303(c) of the CWA.

This Methodology does not substitute for the CWA or EPA's regulations; nor is it a regulation itself. Thus, the 2000 Human Health Methodology cannot impose legally-binding requirements on EPA, States, Tribes or the regulated community, and may not apply to a particular situation based upon the circumstances. EPA and State/Tribal decision-makers retain the discretion to use different, scientifically defensible, methodologies to develop human health criteria on a case-by-case basis that differ from this Methodology where appropriate. EPA may change the Methodology in the future through intermittent refinements as advances in science or changes in Agency policy occur.

The 2000 Human Health Methodology incorporates scientific advancements made over the past two decades. The use of this Methodology is an important component of the Agency's efforts to improve the quality of the Nation's waters. EPA believes the Methodology will enhance the overall scientific basis of water quality criteria. Further, the Methodology should help States and Tribes address their unique water quality issues and risk management decisions, and afford them greater flexibility in developing their water quality programs.

There are three companion Technical Support Document (TSD) volumes for the 2000 Human Health Methodology: a Risk Assessment TSD; an Exposure Assessment TSD; and a Bioaccumulation TSD. These documents are intended to further support States and Tribes in developing AWQC to reflect local conditions. The Risk Assessment TSD (USEPA, 2000) is being published concurrently with this Methodology. Publication of the Exposure Assessment and Bioaccumulation TSDs are anticipated in 2001.

1.3 HISTORY OF THE AMBIENT WATER QUALITY CRITERIA (AWQC) METHODOLOGY

In 1980, EPA published AWQC for 64 pollutants/pollutant classes identified in Section 307(a) of the CWA and provided a methodology for deriving the criteria (USEPA, 1980). These 1980 AWQC National Guidelines (or the "1980 Methodology") for developing AWQC for the protection of human health addressed three types of endpoints: noncancer, cancer, and organoleptic (taste and odor) effects. Criteria for protection against noncancer and cancer effects were estimated by using risk assessment-based procedures, including extrapolation from animal toxicity or human epidemiological studies. Basic human exposure assumptions were applied to the criterion equation.

The risk assessment-based procedures used to derive the AWQC to protect human health were specific to whether the endpoint was cancer or noncancer. When using cancer as the critical risk assessment endpoint (which had been assumed not to have a threshold), the AWQC were presented as a range of concentrations associated with specified incremental lifetime risk

levels[1]. When using noncancer effects as the critical endpoint, the AWQC reflected an assessment of a "no-effect" level, since noncancer effects were assumed to have a threshold. The key features of each procedure are described briefly in the following paragraphs.

Cancer effects. If human or animal studies on a contaminant indicated that it induced a statistically significant carcinogenic response, the 1980 AWQC National Guidelines treated the contaminant as a carcinogen and derived a low-dose cancer potency factor from available animal data using the linearized multistage model (LMS). The LMS, which uses a linear, nonthreshold assumption for low-dose risk, was used by the Agency as a science policy choice in protecting public health, and represented a plausible upper limit for low-dose risk. The cancer potency factor, which expresses incremental, lifetime risk as a function of the rate of intake of the contaminant, was then combined with exposure assumptions to express that risk in terms of an ambient water concentration. In the 1980 AWQC National Guidelines, the Agency presented a range of contaminant concentrations corresponding to incremental cancer risks of 10^{-7} to 10^{-5} (that is, a risk of one additional case of cancer in a population of ten million to one additional cancer case in a population of one hundred thousand, respectively).

Noncancer effects. If the pollutant was not considered to have the potential for causing cancer in humans (later defined as a known, probable, or possible human carcinogen by the 1986 *Guidelines for Carcinogen Risk Assessment,* USEPA, 1986d), the 1980 AWQC National Guidelines treated the contaminant as a noncarcinogen; a criterion was derived using a threshold concentration for noncancer adverse effects. The criteria derived from noncancer data were based on the Acceptable Daily Intake (ADI) (now termed the reference dose [RfD]). ADI values were generally derived using a no-observed-adverse-effect level (NOAEL) from animal studies, although human data were used whenever available. The ADI was calculated by dividing the NOAEL by an uncertainty factor to account for uncertainties inherent in extrapolating limited toxicological data to humans. In accordance with the National Research Council recommendations of 1977 (NRC, 1977), safety factors (SFs) (later redefined as uncertainty factors) of 10, 100, or 1,000 were used, depending on the quality of the data.

Organoleptic effects. Organoleptic characteristics were also used in developing criteria for some contaminants to control undesirable taste and/or odor imparted by them to ambient water. In some cases, a water quality criterion based on organoleptic effects would be more stringent than a criterion based on toxicologic endpoints. The 1980 AWQC National Guidelines emphasized that criteria derived for organoleptic endpoints are not based on toxicological information, have no direct relationship to adverse human health effects and, therefore, do not necessarily represent approximations of acceptable risk levels for humans.

[1]Throughout this document, the term "risk level" regarding a cancer assessment using linear approach refers to an upper-bound estimate of excess lifetime cancer risk.

1.4 RELATIONSHIP OF WATER QUALITY STANDARDS TO AWQC

Under Section 303(c) of the CWA, States have the primary responsibility for establishing water quality standards, defined under the Act as designated beneficial uses of a water segment and the water quality criteria necessary to support those uses. Additionally, Native American Tribes authorized to administer the water quality standards program under 40 CFR 131.8 establish water quality standards for waters within their jurisdictions. This statutory framework allows States and authorized Tribes to work with local communities to adopt appropriate designated uses and to adopt criteria to protect those designated uses. Section 303(c) provides for EPA review of water quality standards and for promulgation of a superseding Federal rule in cases where State or Tribal standards are not consistent with the applicable requirements of the CWA and the implementing Federal regulations, or where the Agency determines Federal standards are necessary to meet the requirements of the Act. Section 303(c)(2)(B) specifically requires States and authorized Tribes to adopt water quality criteria for toxics for which EPA has published criteria under Section 304(a) and for which the discharge or presence could reasonably be expected to interfere with the designated use adopted by the State or Tribe. In adopting such criteria, States and authorized Tribes must establish numerical values based on one of the following: (1) 304(a) criteria; (2) 304(a) criteria modified to reflect site-specific conditions; or, (3) other scientifically defensible methods. In addition, States and authorized Tribes can establish narrative criteria where numeric criteria cannot be determined.

It must be recognized that the Act uses the term "criteria" in two different ways. In Section 303(c), the term is part of the definition of a water quality standard. Specifically, a water quality standard is composed of designated uses and the criteria necessary to protect those uses. Thus, States and authorized Tribes are required to adopt regulations which contain legally enforceable criteria. However, in Section 304(a) the term criteria is used to describe the scientific information that EPA develops to be used as guidance by States, authorized Tribes and EPA when establishing water quality standards pursuant to 303(c). Thus, two distinct purposes are served by the 304(a) criteria. The first is as guidance to the States and authorized Tribes in the development and adoption of water quality criteria which will protect designated uses, and the second is as the basis for promulgation of a superseding Federal rule when such action is necessary.

1.5 NEED FOR THE AWQC METHODOLOGY REVISIONS

Since 1980, EPA risk assessment practices have evolved significantly in all of the major Methodology areas: that is, cancer and noncancer risk assessments, exposure assessments, and bioaccumulation. When the 1980 Methodology was developed, EPA had not yet developed formal cancer or noncancer risk assessment guidelines. Since then, EPA has published several risk assessment guidelines. In cancer risk assessment, there have been advances in the use of mode of action (MOA) information to support both the identification of potential human carcinogens and the selection of procedures to characterize risk at low, environmentally relevant exposure levels. EPA published *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA, 1996a, hereafter the "1996 proposed cancer guidelines"). These guidelines presented revised procedures to quantify cancer risk at low doses, replacing the current default use of the LMS model. Following review by the Agency's Science Advisory Board (SAB), EPA published the

revised *Guidelines for Carcinogen Risk Assessment–Review Draft* in July 1999 (USEPA, 1999a, hereafter the "1999 draft revised cancer guidelines"). In noncancer risk assessment, the Agency is moving toward the use of the benchmark dose (BMD) and other dose-response approaches in place of the traditional NOAEL approach to estimate an RfD or Reference Concentration (RfC). *Guidelines for Mutagenicity Risk Assessment* were published in 1986 (USEPA, 1986b). In 1991, the Agency published *Guidelines for Developmental Toxicity Risk Assessment* (USEPA, 1991), and it issued *Guidelines for Reproductive Toxicity Risk Assessment* in 1996 (USEPA, 1996b). In 1998, EPA published final *Guidelines for Neurotoxicity Risk Assessment* (USEPA, 1998), and in 1999 it issued the draft *Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA, 1999b).

In 1986, the Agency made available to the public the Integrated Risk Information System (IRIS). IRIS is a database that contains risk information on the cancer and noncancer effects of chemicals. The IRIS assessments are peer reviewed and represent EPA consensus positions across the Agency's program and regional offices.

New studies have addressed water consumption and fish tissue consumption. These studies provide a more current and comprehensive description of national, regional, and special-population consumption patterns that EPA has reflected in the 2000 Human Health Methodology. In addition, more formalized procedures are now available to account for human exposure from multiple sources when setting health goals such as AWQC that address only one exposure source. In 1986, the Agency published the *Total Exposure Assessment Methodology (TEAM) Study: Summary and Analysis, Volume I, Final Report* (USEPA, 1986c), which presents a process for conducting comprehensive evaluation of human exposures. In 1992, EPA published the revised *Guidelines for Exposure Assessment* (USEPA, 1992), which describe general concepts of exposure assessment, including definitions and associated units, and provide guidance on planning and conducting an exposure assessment. The *Exposure Factors Handbook* was updated in 1997 (USEPA, 1997a). Also in 1997, EPA developed *Guiding Principles for Monte Carlo Analysis* (USEPA, 1997b) and published its *Policy for Use of Probabilistic Analysis in Risk Assessment* (see http://www.epa.gov/ncea/mcpolicy.htm). The Monte Carlo guidance can be applied to exposure assessments and risk assessments. The Agency has recently developed the Relative Source Contribution (RSC) Policy for assessing total human exposure to a contaminant and apportioning the RfD among the media of concern, published for the first time in this Methodology.

The Agency has moved toward the use of a bioaccumulation factor (BAF) to reflect the uptake of a contaminant from all sources (e.g., ingestion, sediment) by fish and shellfish, rather than just from the water column as reflected by the use of a bioconcentration factor (BCF) in the 1980 Methodology. The Agency has also developed detailed procedures and guidelines for estimating BAF values.

Another reason for the 2000 Human Health Methodology is the need to bridge the gap between the differences in the risk assessment and risk management approaches used by EPA's Office of Water for the derivation of AWQC under the authority of the CWA and Maximum Contaminant Level Goals (MCLGs) under the Safe Drinking Water Act (SDWA). Three notable differences are the treatment of chemicals designated as Group C, possible human carcinogens

under the 1996 proposed cancer guidelines, the consideration of non-water sources of exposure when setting an AWQC or MCLG for a noncarcinogen, and cancer risk ranges. Those three differences are described in the three subsections below, respectively.

1.5.1 Group C Chemicals

Chemicals were typically classified as Group C–i.e., possible human carcinogens–under the existing (1986) EPA cancer classification scheme for any of the following reasons:

1) Carcinogenicity has been documented in only one test species and/or only one cancer bioassay and the results do not meet the requirements of "sufficient evidence."

2) Tumor response is of marginal statistical significance due to inadequate design or reporting.

3) Benign, but not malignant, tumors occur with an agent showing no response in a variety of short-term tests for mutagenicity.

4) There are responses of marginal statistical significance in a tissue known to have a high or variable background rate.

The 1986 *Guidelines for Carcinogen Risk Assessment* (hereafter the "1986 cancer guidelines") specifically recognized the need for flexibility with respect to quantifying the risk of Group C, possible human carcinogens. The 1986 cancer guidelines noted that agents judged to be in Group C, possible human carcinogens, may generally be regarded as suitable for quantitative risk assessment, but that case-by-case judgments may be made in this regard.

The EPA Office of Water has historically treated Group C chemicals differently under the CWA and the SDWA. It is important to note that the 1980 AWQC National Guidelines for setting AWQC under the CWA predated EPA's carcinogen classification system, which was proposed in 1984 (USEPA, 1984) and finalized in 1986 (USEPA, 1986a). The 1980 AWQC National Guidelines did not explicitly differentiate among agents with respect to the weight of evidence for characterizing them as likely to be carcinogenic to humans. For all pollutants judged as having adequate data for quantifying carcinogenic risk–including those now classified as Group C–AWQC were derived based on data on cancer incidence. In the1980 AWQC National Guidelines, EPA emphasized that the AWQC for carcinogens should state that the recommended concentration for maximum protection of human health is zero. At the same time, the criteria published for specific carcinogens presented water concentrations for these pollutants corresponding to individual lifetime excess cancer risk levels in the range of 10^{-7} to 10^{-5}.

In the development of national primary drinking water regulations under the SDWA, EPA is required to promulgate a health-based MCLG for each contaminant. The Agency policy has been to set the MCLG at zero for chemicals with strong evidence of carcinogenicity associated with exposure from water. For chemicals with limited evidence of carcinogenicity, including many Group C agents, the MCLG was usually obtained using an RfD based on the

pollutant's noncancer effects with the application of an additional uncertainty factor of 1 to 10 to account for carcinogenic potential of the chemical. If valid noncancer data for a Group C agent were not available to establish an RfD but adequate data are available to quantify the cancer risk, then the MCLG was based upon a nominal lifetime excess cancer risk in the range of 10^{-6} to10^{-5} (ranging from one case in a population of one million to one case in a population of one hundred thousand). Even in those cases where the RfD approach has been used for the derivation of the MCLG for a Group C agent, the drinking water concentrations associated with excess cancer risks in the range of 10^{-6} to 10^{-5} were also provided for comparison.

It should also be noted that EPA's pesticides program has applied both of the previously described methods for addressing Group C chemicals in actions taken under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and finds both methods applicable on a case-by-case basis. Unlike the drinking water program, however, the pesticides program does not add an extra uncertainty factor to account for potential carcinogenicity when using the RfD approach.

In the 1999 draft revised cancer guidelines, there are no more alphanumeric categories. Instead, there will be longer narratives for hazard characterization that will use consistent descriptive terms when assessing cancer risk.

1.5.2 Consideration of Non-water Sources of Exposure

The 1980 AWQC National Guidelines recommended that contributions from non-water sources, namely air and non-fish dietary intake, be subtracted from the Acceptable Daily Intake (ADI), thus reducing the amount of the ADI "available" for water-related sources of intake. In practice, however, when calculating human health criteria, these other exposures were generally not considered because reliable data on these exposure pathways were not available. Consequently, the AWQC were usually derived such that drinking water and fish ingestion accounted for the entire ADI (now called RfD).

In the drinking water program, a similar "subtraction" method was used in the derivation of MCLGs proposed and promulgated in drinking water regulations through the mid-1980s. More recently, the drinking water program has used a "percentage" method in the derivation of MCLGs for noncarcinogens. In this approach, the percentage of total exposure typically accounted for by drinking water, referred to as the relative source contribution (RSC), is applied to the RfD to determine the maximum amount of the RfD "apportioned" to drinking water reflected by the MCLG value. In using this percentage procedure, the drinking water program also applies a ceiling level of 80 percent of the RfD and a floor level of 20 percent of the RfD. That is, the MCLG cannot account for more than 80 percent of the RfD, nor less than 20 percent of the RfD.

The drinking water program usually takes a conservative approach to public health by applying an RSC factor of 20 percent to the RfD when adequate exposure data do not exist, assuming that the major portion (80 percent) of the total exposure comes from other sources, such as diet.

In the 2000 Human Health Methodology, guidance for the routine consideration of non-water sources of exposure [both ingestion exposures (e.g., food) and exposures other than the oral route (e.g., inhalation)] is presented. The approach is called the Exposure Decision Tree. Relative source contribution estimates will be made by EPA using this approach, which allows for use of either the subtraction or percentage methods, depending on chemical-specific circumstances, within the 20 to 80 percent range described above.

1.5.3 Cancer Risk Ranges

In addition to the different risk assessment approaches discussed above for deriving AWQC and MCLGs for Group C agents, there have been different risk management approaches by the drinking water and surface water programs on lifetime excess risk values when setting health-based criteria for carcinogens. The surface water program has derived AWQC for carcinogens that generally corresponded to lifetime excess cancer risk levels of 10^{-7} to 10^{-5}. The drinking water program has set MCLGs for Group C agents based on a slightly less stringent risk range of 10^{-6} to 10^{-5}, while MCLGs for chemicals with strong evidence of carcinogenicity (that is, classified as Group A, known, or B probable, human carcinogen) are set at zero. The drinking water program is now following the principles of the 1999 draft revised cancer guidelines to determine the type of low-dose extrapolation based on mode of action.

It is also important to note that under the drinking water program, for those substances having an MCLG of zero, enforceable Maximum Contaminant Levels (MCLs) have generally been promulgated to correspond with cancer risk levels ranging from 10^{-6} to 10^{-4}. Unlike AWQC and MCLGs which are strictly health-based criteria, MCLs are developed with consideration given to the costs and technological feasibility of reducing contaminant levels in water to meet those standards.

With the 2000 Human Health Methodology, EPA will publish its national 304(a) water quality criteria at a 10^{-6} risk level, which EPA considers appropriate for the general population. EPA is increasing the degree of consistency between the drinking water and ambient water programs, given the somewhat different requirements of the CWA and SDWA.

1.6 OVERVIEW OF THE AWQC METHODOLOGY REVISIONS

The following equations for deriving AWQC include toxicological and exposure assessment parameters which are derived from scientific analysis, science policy, and risk management decisions. For example, values for parameters such as a field-measured BAF or a point of departure from an animal study [in the form of a lowest-observed-adverse-effect level (LOAEL)/no-observed -adverse-effect level (NOAEL)/lower 95 percent confidence limit on a dose associated with a 10 percent extra risk (LED_{10})] are empirically measured using scientific methods. By contrast, the decision to use animal effects as surrogates for human effects involves judgment on the part of the EPA (and similarly, by other agencies) as to the best practice to follow when human data are lacking. Such a decision is, therefore, a matter of science policy. The choice of default fish consumption rates for protection of a certain percentage (i.e., the 90th percentile) of the general population is clearly a risk management decision. In many cases, the Agency has selected parameter values using its best judgment regarding the overall protection afforded by the resulting AWQC when all parameters are combined. For a longer discussion of the differences between science, science policy, and risk management, please refer to Section 2 of this document. Section 2 also provides further details with regard to risk characterization for this Methodology, with emphasis placed on explaining the uncertainties in the overall risk assessment.

The generalized equations for deriving AWQC based on noncancer effects are:

Noncancer Effects[2]

$$AWQC = RfD \cdot RSC \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right) \qquad \text{(Equation 1-1)}$$

Cancer Effects: Nonlinear Low-Dose Extrapolation

$$AWQC = \frac{POD}{UF} \cdot RSC \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right) \qquad \text{(Equation 1-2)}$$

[2] Although appearing in this equation as a factor to be multiplied, the RSC can also be an amount subtracted. Refer to the explanation key below the equations.

Cancer Effects: Linear Low-Dose Extrapolation

$$AWQC = RSD \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right) \qquad \text{(Equation 1-3)}$$

where:

AWQC	=	Ambient Water Quality Criterion (mg/L)
RfD	=	Reference dose for noncancer effects (mg/kg-day)
POD	=	Point of departure for carcinogens based on a nonlinear low-dose extrapolation (mg/kg-day), usually a LOAEL, NOAEL, or LED_{10}
UF	=	Uncertainty Factor for carcinogens based on a nonlinear low-dose extrapolation (unitless)
RSD	=	Risk-specific dose for carcinogens based on a linear low-dose extrapolation (mg/kg-day) (dose associated with a target risk, such as 10^{-6})
RSC	=	Relative source contribution factor to account for non-water sources of exposure. (Not used for linear carcinogens.) May be either a percentage (multiplied) or amount subtracted, depending on whether multiple criteria are relevant to the chemical.
BW	=	Human body weight (default = 70 kg for adults)
DI	=	Drinking water intake (default = 2 L/day for adults)
FI_i	=	Fish intake at trophic level (TL) I (I = 2, 3, and 4) (defaults for total intake = 0.0175 kg/day for general adult population and sport anglers, and 0.1424 kg/day for subsistence fishers). Trophic level breakouts for the general adult population and sport anglers are: TL2 = 0.0038 kg/day; TL3 = 0.0080 kg/day; and TL4 = 0.0057 kg/day.
BAF_i	=	Bioaccumulation factor at trophic level I (I=2, 3 and 4), lipid normalized (L/kg)

For highly bioaccumulative chemicals where ingestion from water might be considered negligible, EPA is currently evaluating the feasibility of developing and implementing AWQCs that are expressed in terms of concentrations in tissues of aquatic organisms. Such tissue residue criteria might be used as an alternative to AWQCs which are expressed as concentrations in water, particularly in situations where AWQCs are at or below the practical limits for quantifying a chemical in water. Even though tissue residue criteria would not require the use of a BAF in their derivation, implementing such criteria would still require a mechanism for relating chemical loads and concentrations in water and sediment to concentrations in tissues of appropriate fish and shellfish (e.g., a BAF or bioaccumulation model). At this time, no revisions are planned to the Methodology to provide specific guidance on developing fish tissue-based water quality criteria. However, guidance may be provided in the future either as a separate document or integrated in a specific 304(a) water quality criteria document for a chemical that warrants such an approach.

AWQC for the protection of human health are designed to minimize the risk of adverse effects occurring to humans from chronic (lifetime) exposure to substances through the ingestion of drinking water and consumption of fish obtained from surface waters. The Agency is not recommending the development of additional water quality criteria similar to the "drinking water health advisories" that focus on acute or short-term effects; these are not seen as routinely having a meaningful role in the water quality criteria and standards program. However, as discussed below, there may be some instances where the consideration of acute or short-term toxicity and exposure in the derivation of AWQC is warranted.

Although the AWQC are based on chronic health effects data (both cancer and noncancer effects), the criteria are intended to also be protective against adverse effects that may reasonably be expected to occur as a result of elevated acute or short-term exposures. That is, through the use of conservative assumptions with respect to both toxicity and exposure parameters, the resulting AWQC should provide adequate protection not only for the general population over a lifetime of exposure, but also for special subpopulations who, because of high water- or fish-intake rates, or because of biological sensitivities, have an increased risk of receiving a dose that would elicit adverse effects. The Agency recognizes that there may be some cases where the AWQC based on chronic toxicity may not provide adequate protection for a subpopulation at special risk from shorter-term exposures. The Agency encourages States, Tribes, and others employing the 2000 Human Health Methodology to give consideration to such circumstances in deriving criteria to ensure that adequate protection is afforded to all identifiable subpopulations. (See Section 4.3, Factors Used in the AWQC Computation, for additional discussion of these subpopulations.)

The EPA is in the process of revising its cancer guidelines, including its descriptions of human carcinogenic potential. Once final guidelines are published, they will be the basis for assessment under this methodology. In the meanwhile, the 1986 guidelines are used and extended with principles discussed in EPA's 1999 *Guidelines for Carcinogen Risk Assessment - Review Draft* (hereafter "1999 draft revised cancer guidelines"). These principles arise from new science about cancer discovered in the last 15 years and from EPA policy of recent years supporting full characterization of hazard and risk both for the general population and potentially sensitive groups such as children. These principles are incorporated in recent and ongoing assessments such as the reassessment of dioxin, consistent with the 1986 guidelines. Until final guidelines are published, information is presented to describe risk under both the old guidelines and draft revisions. Dose-response assessment under the 1986 guidelines employs a linearized multistage model to extrapolate tumor dose-response observed in animal or human studies down to zero dose, zero extra risk. The dose-response assessment under EPA's 1999 draft revised cancer guidelines is a two-step process. In the first step, the response data are modeled in the range of empirical observation. Modeling in the observed range is done with biologically based or appropriate curve-fitting modeling. In the second step, extrapolation below the range of observation is accomplished by biologically based modeling if there are sufficient data or by a default procedure (linear, nonlinear, or both). A point of departure (POD) for extrapolation is estimated from modeling observed data. The lower 95 percent confidence limit on a dose associated with 10 percent extra risk (LED_{10}) is the standard POD for low-dose extrapolation. The linear default procedure is a straight line extrapolation to the origin (i.e., zero dose, zero extra risk) from the POD, which is the LED_{10} identified in the observable response

range. The result of this procedure is generally comparable (within 2-fold) to that of using a linearized multistage model under existing, 1986 guidelines. The linear low-dose extrapolation applies to agents that are best characterized by the assumption of linearity (e.g., direct DNA reactive mutagens) for their MOA. A linear approach would also be applied when inadequate or no information is available to explain the carcinogenic MOA; this is a science policy choice in the interest of public health. If it is determined that the MOA understanding fully supports a nonlinear extrapolation, the AWQC is derived using the nonlinear default which is based on a margin of exposure (MOE) analysis using the LED_{10} as the POD and applying uncertainty factors (UFs) to arrive at an acceptable MOE. There may be situations where it is appropriate to apply both the linear and nonlinear default procedures (e.g., for an agent that is both DNA reactive and active as a promoter at higher doses).

For substances that are carcinogenic, particularly those for which the MOA suggests nonlinearity at low doses, the Agency recommends that an integrated approach be taken in looking at cancer and noncancer effects. If one effect does not predominate, AWQC values should be determined for both carcinogenic and noncarcinogenic endpoints. The lower of the resulting values should be used for the AWQC.

When deriving AWQC for noncarcinogens and carcinogens based on a nonlinear low-dose extrapolation, a factor is included to account for other non-water exposure sources [both ingestion exposures (e.g., food) and exposures other than the oral route (e.g., inhalation)] so that the entire RfD, or POD/UF, is not apportioned to drinking water and fish consumption alone. Guidance is provided in the 2000 Human Health Methodology for determining the factor (i.e., the RSC) to be used for a particular chemical. The Agency is recommending the use of an Exposure Decision Tree procedure to support the determination of the appropriate RSC value for a given water contaminant. In the absence of data, the Agency intends to use 20 percent of the RfD (or POD/UF) as the default RSC in calculating 304(a) criteria or promulgating State or Tribal water quality standards under Section 303(c).

With AWQC derived for carcinogens based on a linear low-dose extrapolation, the Agency will publish recommended criteria values at a 10^{-6} risk level. States and authorized Tribes can always choose a more stringent risk level, such as 10^{-7}. EPA also believes that criteria based on a 10^{-5} risk level are acceptable for the general population as long as States and authorized Tribes ensure that the risk to more highly exposed subgroups (sportfishers or subsistence fishers) does not exceed the 10^{-4} level. Clarification on this risk management decision is provided in Section 2 of this document.

The default fish consumption value for the general adult population in the 2000 Human Health Methodology is 17.5 grams/day, which represents an estimate of the 90th percentile consumption rate for the U.S. adult population based on the U.S. Department of Agriculture's (USDA's) Continuing Survey of Food Intake by Individuals (CSFII) 1994-96 data (USDA, 1998). EPA will use this default intake rate with future national 304(a) criteria derivations or revisions. This default value is chosen to be protective of the majority of the general population. However, States and authorized Tribes are urged to use a fish intake level derived from local data on fish consumption in place of this default value when deriving AWQC, ensuring that the fish intake level chosen is protective of highly exposed individuals in the population. EPA has

provided default values for States and authorized Tribes that do not have adequate information on local or regional consumption patterns, based on numerous studies that EPA has reviewed on sport anglers and subsistence fishers. EPA's defaults for these population groups are estimates of their average consumption. EPA recommends a default of 17.5 grams/day for sport anglers as an approximation of their average consumption and 142.4 grams/day for subsistence fishers, which falls within the range of averages for this group. Consumption rates for women of childbearing age and children younger than 14 are also provided to maximize protection in those cases where these subpopulations may be at greatest risk.

In the 2000 Human Health Methodology, criteria are derived using a BAF rather than a BCF. To derive the BAF, States and authorized Tribes may use EPA's Methodology or any method consistent with this Methodology. EPA's highest preference in developing BAFs are BAFs based on field-measured data from local/regional fish.

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USEPA (U.S. Environmental Protection Agency). 2000. *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). Technical Support Document Volume 1: Risk Assessment.* Office of Science and Technology, Office of Water. Washington, DC. EPA-822-B-00-005. August.

2. CLARIFICATIONS ON THE METHODOLOGY, RISK CHARACTERIZATION, AND OTHER ISSUES FOR DEVELOPING CRITERIA

2.1 IDENTIFYING THE POPULATION SUBGROUP THAT THE AWQC SHOULD PROTECT

Water quality criteria are derived to establish ambient concentrations of pollutants which, if not exceeded, will protect the general population from adverse health impacts from those pollutants due to consumption of aquatic organisms and water, including incidental water consumption related to recreational activities. For each pollutant, chronic criteria are derived to reflect long-term consumption of food and water. An important decision to make when setting AWQC is the choice of the particular population to protect. For instance, criteria could be set to protect those individuals who have average or "typical" exposures, or the criteria could be set so that they offer greater protection to those individuals who are more highly exposed. EPA has selected default parameter values that are representative of several defined populations: adults in the general population; sport (recreational) fishers; subsistence fishers; women of childbearing age (defined as ages 15-44); and children (up to the age of 14). In deciding on default parameter values, EPA is aware that multiple parameters are used in combination when calculating AWQC (e.g., intake rates and body weight). EPA describes the estimated population percentiles that are represented by each of the default exposure parameter values in Section 4.

EPA's national 304(a) criteria are usually derived to protect the majority of the general population from chronic adverse health effects. EPA has used a combination of median values, mean values, and percentile estimates for the parameter value defaults to calculate its national 304(a) criteria. EPA believes that its assumptions afford an overall level of protection targeted at the high end of the general population (i.e., the target population or the criteria-basis population). EPA also believes that this is reasonably conservative and appropriate to meet the goals of the CWA and the 304(a) criteria program. EPA considers that its target protection goal is satisfied if the population as a whole will be adequately protected by the human health criteria when the criteria are met in ambient water. However, associating the derived criteria with a specific population percentile is far more difficult, and such a quantitative descriptor typically requires detailed distributional exposure and dose information. EPA's *Guidelines For Exposure Assessment* (USEPA, 1992) describes the extreme difficulty in making accurate estimates of exposures and indicates that uncertainties at the more extreme ends of the distribution increase greatly. On quantifying population exposures/risks, the guidelines specifically state:

> *In practice, it is difficult even to establish an accurate mean health effect risk for a population. This is due to many complications, including uncertainties in using animal data for human dose-response relationships, nonlinearities in the dose-response curve, projecting incidence data from one group to another dissimilar group, etc. Although it has been common practice to estimate the number of cases of disease, especially cancer, for populations exposed to chemicals, it should be understood that these estimates are not meant to be accurate estimates of real (or actuarial) cases of disease. The estimate's value lies in framing*

hypothetical risk in an understandable way rather than in any literal interpretation of the term "cases."

Although it is not possible to subject the estimates to such a rigorous analysis (say, for example, to determine what criterion value provides protection of exactly the 90th percentile of the population), EPA believes that the combination of parameter value assumptions achieves its target goal, without being inordinately conservative. The standard assumptions made for the national 304(a) criteria are as follows. The assumed body weight value used is an arithmetic mean, as are the RSC intake estimates of other exposures (e.g., non-fish dietary), when data are available. The BAF component data (e.g., for lipid values, for particulate and dissolved organic carbon) are based on median (i.e., 50th percentile) values. The drinking water intake values are approximately 90th percentile estimates and fish intake values are 90th percentile estimates. EPA believes the use of these values will result in 304(a) criteria that are protective of a majority of the population; this is EPA's goal.

However, EPA also strongly believes that States and authorized Tribes should have the flexibility to develop criteria, on a site-specific basis, that provide additional protection appropriate for highly exposed populations. EPA is aware that exposure patterns in general, and fish consumption in particular, vary substantially. EPA understands that highly exposed populations may be widely distributed geographically throughout a given State or Tribal area. EPA recommends that priority be given to identifying and adequately protecting the most highly exposed population. Thus, if the State or Tribe determines that a highly exposed population is at greater risk and would not be adequately protected by criteria based on the general population, and by the national 304(a) criteria in particular, EPA recommends that the State or Tribe adopt more stringent criteria using alternative exposure assumptions.

EPA has provided recommended default intake rates for various population groups for State and Tribal consideration. EPA does not intend for these alternative default values to be prescriptive. EPA strongly emphasizes its preference that States and Tribes use local or regional data over EPA's defaults, if they so choose, as being more representative of their population groups of concern.

In the course of updating the 2000 Human Health Methodology, EPA received some questions regarding the population groups for which the criteria would be developed. EPA does not intend to derive multiple 304(a) criteria for all subpopulation groups for every chemical. As stated above, criteria that address chronic adverse health effects are most applicable to the CWA Section 304(a) criteria program and the chemicals evaluated for this program. If EPA determined that pregnant women/fetuses or young children were the target population (or criteria basis population) of a chemical's RfD or POD/UF, then the 304(a) criteria would be developed using exposure parameters for that subgroup. This would only be relevant for acute or subchronic toxicity situations. This does not conflict with the fact that chronic health effects potentially reflect a person's exposure during both childhood and adult years.

For RfD-based and POD/UF-based chemicals, EPA's policy is that, in general, the RfD (or POD/UF) should not be exceeded and the exposure assumptions used should reflect the population of concern. It is recommended that when a State or authorized Tribe sets a

waterbody-specific AWQC, they consider the populations most exposed via water and fish. EPA's policy on cancer risk management goals is discussed in Section 2.4.

Health Risks to Children

In recognition that children have a special vulnerability to many toxic substances, EPA's Administrator directed the Agency in 1995 to explicitly and consistently take into account environmental health risks to infants and children in all risk assessments, risk characterizations, and public health standards set for the United States. In April 1997, President Clinton signed Executive Order 13045 on the protection of children from environmental health risks, which assigned a high priority to addressing risks to children. In May 1997, EPA established the Office of Children's Health Protection to ensure the implementation of the President's Executive Order. EPA has increased efforts to ensure its guidance and regulations take into account risks to children. Circumstances where risks to children should be considered in the context of the 2000 Human Health Methodology are discussed in the Section 3.2, Noncancer Effects (in terms of developmental and reproductive toxicity) and in Section 4, Exposure (for appropriate exposure intake parameters).

Details on risk characterization and the guiding principles stated above are included in EPA's March 21, 1995 policy statement and the discussion of risk characterization (USEPA, 1995) and the 1999 *Guidelines for Carcinogen Risk Assessment. Review Draft* (USEPA, 1999a) and the *Reproductive and Toxicity Risk Assessment Guidelines* of 1996 (USEPA, 1996b).

2.2 SCIENCE, SCIENCE POLICY, AND RISK MANAGEMENT

An important part of risk characterization, as described later in Section 2.7, is to make risk assessments transparent. This means that conclusions drawn from the science are identified separately from policy judgments and risk management decisions, and that the use of default values or methods, as well as the use of assumptions in risk assessments, are clearly articulated. In this Methodology, EPA has attempted to separate scientific analysis from science policy and risk management decisions for clarity. This should allow States and Tribes (who are also prospective users of this Methodology) to understand the elements of the Methodology accurately and clearly, and to easily separate out the scientific decisions from the science policy and risk management decisions. This is important so that when questions are asked regarding the scientific merit, validity, or apparent stringency or leniency of AWQC, the implementer of the criteria can clearly explain what judgments were made to develop the criterion in question and to what degree these judgments were based on science, science policy, or risk management. To some extent this process will also be displayed in future AWQC documents.

When EPA speaks of science or scientific analysis, it is referring to the extraction of data from toxicological or exposure studies and surveys with a minimum of judgment being used to make inferences from the available evidence. For example, if EPA is describing a POD from an animal study (e.g., a LOAEL), this is usually determined as a lowest dose that produces an observable adverse effect. This would constitute a scientific determination. Judgments applying science policy, however, may enter this determination. For example, several scientists may differ in their opinion of what is adverse, and this in turn can influence the selection of a LOAEL

in a given study. The use of an animal study to predict effects in a human in the absence of human data is an inherent science policy decision. The selection of specific UFs when developing an RfD is another example of science policy. In any risk assessment, a number of decision points occur where risk to humans can only be inferred from the available evidence. Both scientific judgments and policy choices may be involved in selecting from among several possible inferences when conducting a risk assessment.

Risk management is the process of selecting the most appropriate guidance or regulatory actions by integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision. In this Methodology, the choice of a default fish consumption rate which is protective of 90 percent of the general population is a risk management decision. The choice of an acceptable cancer risk by a State or Tribe is a risk management decision.

Many of the components in the 2000 Human Health Methodology are an amalgam of science, science policy, and/or risk management. For example, most of the default values chosen by EPA are based on examination of scientific data and application of either science policy or risk management. This includes the default assumption of 2 liters a day of drinking water; the assumption of 70 kilograms for an adult body weight; the use of default percent lipid and particulate organic carbon/dissolved organic carbon (POC/DOC) for developing national BAFs; the default fish consumption rates for the general population and sport and subsistence anglers; and the choice of a default cancer risk level. Some decisions are more grounded in science and science policy (such as the choice of default BAFs) and others are more obviously risk management decisions (such as the determination of default fish consumption rates and cancer risk levels). Throughout the 2000 Human Health Methodology, EPA has identified the kind of decision necessary to develop defaults and what the basis for the decision was. More details on the concepts of science analysis, science policy, risk management, and how they are introduced into risk assessments are included in *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983).

2.3 SETTING CRITERIA TO PROTECT AGAINST MULTIPLE EXPOSURES FROM MULTIPLE CHEMICALS (CUMULATIVE RISK)

EPA is very much aware of the complex issues and implications of cumulative risk and has endeavored to begin developing an overall approach at the Agency-wide level. Assuming that multiple exposures to multiple chemicals are additive is scientifically sound if they exhibit the same toxic endpoints and modes of action. There are numerous publications relevant to cumulative risk that can assist States and Tribes in understanding the complex issues associated with cumulative risk. These include the following:

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- Hertzberg, R.C., G. Rice, and L.K. Teuschler. 1999. Methods for health risk assessment of combustion mixtures. In: *Hazardous Waste Incineration: Evaluating the Human*

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The Agency's program offices are also engaged in on-going discussions of the great complexities, methodological challenges, data adequacy needs and other information gaps, as well as the science policy and risk management decisions that will need to be made, as they pursue developing a sound strategy and, eventually, specific guidance for addressing cumulative

risks. As a matter of internal policy, EPA is committed to refining the Methodology as advances in relevant aspects of the science improve, as part of the water quality criteria program.

2.4 CANCER RISK RANGE

For deriving 304(a) criteria or promulgating water quality criteria for States and Tribes under Section 303(c) based on the 2000 Human Health Methodology, EPA intends to use the 10^{-6} risk level, which the Agency believes reflects an appropriate risk for the general population. EPA's program office guidance and regulatory actions have evolved in recent years to target a 10^{-6} risk level as an appropriate risk for the general population. EPA has recently reviewed the policies and regulatory language of other Agency mandates (e.g., the Clean Air Act Amendments of 1990, the Food Quality Protection Act) and believes the target of a 10^{-6} risk level is consistent with Agency-wide practice.

EPA believes that both 10^{-6} and 10^{-5} may be acceptable for the general population and that highly exposed populations should not exceed a 10^{-4} risk level. States or Tribes that have adopted standards based on criteria at the 10^{-5} risk level can continue to do so, if the highly exposed groups would at least be protected at the 10^{-4} risk level. However, EPA is not automatically assuming that 10^{-5} will protect "the highest consumers" at the 10^{-4} risk level. Nor is EPA advocating that States and Tribes automatically set criteria based on assumptions for highly exposed population groups at the 10^{-4} risk level. The Agency is simply endeavoring to add that a specific determination should be made to ensure that highly exposed groups do not exceed a 10^{-4} risk level. EPA understands that fish consumption rates vary considerably, especially among subsistence populations, and it is such great variation among these population groups that may make either 10^{-6} or 10^{-5} protective of those groups at a 10^{-4} risk level. Therefore, depending on the consumption patterns in a given State or Tribal jurisdiction, a 10^{-6} or 10^{-5} risk level could be appropriate. In cases where fish consumption among highly exposed population groups is of a magnitude that a 10^{-4} risk level would be exceeded, a more protective risk level should be chosen. Such determinations should be made by the State or Tribal authorities and are subject to EPA's review and approval or disapproval under Section 303(c) of the CWA.

Adoption of a 10^{-6} or 10^{-5} risk level, both of which States and authorized Tribes have chosen in adopting water quality standards to date, represents a generally acceptable risk management decision, and EPA intends to continue providing this flexibility to States and Tribes. EPA believes that such State or Tribal decisions are consistent with Section 303(c) if the State or authorized Tribe has identified the most highly exposed subpopulation, has demonstrated that the chosen risk level is adequately protective of the most highly exposed subpopulation, and has completed all necessary public participation. States and authorized Tribes also have flexibility in how they demonstrate this protectiveness and obtain such information. A State or authorized Tribe may use existing information as well as collect new information in making this determination. In addition, if a State or authorized Tribe does not believe that the 10^{-6} risk level adequately protects the exposed subpopulations, water quality criteria based on a more stringent risk level may be adopted. This discretion includes combining the 10^{-6} risk level with fish consumption rates for highly exposed population groups.

It is important to understand that criteria for carcinogens are based on chosen risk levels that inherently reflect, in part, the exposure parameters used to derive those values. Therefore, changing the exposure parameters also changes the risk. Specifically, the incremental cancer risk levels are *relative*, meaning that any given criterion associated with a particular cancer risk level is also associated with specific exposure parameter assumptions (e.g., intake rates, body weights). When these exposure parameter values change, so does the relative risk. For a criterion derived on the basis of a cancer risk level of 10^{-6}, individuals consuming up to 10 times the assumed fish intake rate would not exceed a 10^{-5} risk level. Similarly, individuals consuming up to 100 times the assumed rate would not exceed a 10^{-4} risk level. Thus, for a criterion based on EPA's default fish intake rate (17.5 gm/day) and a risk level of 10^{-6}, those consuming a pound per day (i.e., 454 grams/day) would potentially experience between a 10^{-5} and a 10^{-4} risk level (closer to a 10^{-5} risk level). (Note: Fish consumers of up to 1,750 gm/day would not exceed the 10^{-4} risk level.) If a criterion were based on high-end intake rates and the relative risk of 10^{-6}, then an average fish consumer would be protected at a cancer risk level of approximately 10^{-8}. The point is that the risks for different population groups are not the same.

2.5 MICROBIOLOGICAL AMBIENT WATER QUALITY CRITERIA

Guidance for deriving microbiological AWQC is not a part of this Methodology. In 1986, EPA published *Ambient Water Quality Criteria for Bacteria - 1986* (USEPA, 1986a), which updated and revised bacteriological criteria previously published in 1976 in *Quality Criteria for Water* (USEPA, 1976). The inclusion of guidance for deriving microbiological AWQC was considered in the 1992 national workshop that initiated the effort to revise the 1980 Methodology and was recommended by the SAB in 1993. Since that time, however, efforts separate from these Methodology revisions have addressed microbiological AWQC concerns. The purpose of this section is to briefly describe EPA's current recommendations and activities.

EPA's *Ambient Water Quality Criteria for Bacteria - 1986* recommends the use of *Escherichia coli* and enterococci rather than fecal coliforms (USEPA, 1986a). EPA's criteria recommendations are:

- Fresh water: *E. coli* not to exceed 126/100 ml or enterococci not to exceed 33/100 ml; and

- Marine water: enterococci not to exceed 35/100 ml.

These criteria should be calculated as the geometric mean based on five equally spaced samples taken over a 30-day period.

In addition, EPA recommends that States adopt a single sample maximum, based on the expected frequency of use. No sample taken should exceed this value. EPA specifies appropriate single sample maximum values in the 1986 criteria document.

Current Activities and Plans for Future Work

EPA has identified development of microbial water quality criteria as part of its strategy to control waterborne microbial disease, by controlling pathogens in waterbodies and by protecting designated uses, such as recreation and public water supplies. The program fosters an integrated approach to protect both ground-water and surface water sources. EPA plans to conduct additional monitoring for *Cryptosporidium parvum* and *E. coli*, and determine action plans in accordance with the results of this monitoring.

EPA recommends no change at this time in the stringency of its bacterial criteria for recreational waters; existing criteria and methodologies from 1986 will still apply. The recommended methods for *E. coli* and enterococci have been improved. As outlined in the *Action Plan for Beaches and Recreational Waters* (Beach Action Plan, see below), the Agency plans to conduct national studies on improving indicators together with epidemiology studies for new criteria development (USEPA, 1999b). The Agency is also planning to establish improved temporal and spatial monitoring protocols.

In the Beach Action Plan, EPA identifies a multi-year strategy for monitoring recreational water quality and communicating public health risks associated with potentially pathogen-contaminated recreational rivers, lakes, and ocean beaches. It articulates the Agency's rationale and goals in addressing specific problems and integrates all associated program, policy, and research needs and directions. The Beach Action Plan also provides information on timing, products and lead organization for each activity. These include activities and products in the areas of program development, risk communication, water quality indicator research, modeling and monitoring research, and exposure and health effects research.

Recently, EPA approved new 24-hour *E. coli* and enterococcus tests for recreational waters that may be used as an alternative to the 48-hour test (USEPA, 1997). EPA anticipates proposing these methods for inclusion in the 40 CRF 136 in the Fall of 2000. EPA has also published a video with accompanying manual on the original and newer methods for enterococci and *E. coli* (USEPA, 2000).

As part of the Beach Action Plan, EPA made the following recommendations for further Agency study:

- Future criteria development should consider the risk of diseases other than gastroenteritis. EPA intends to consider and evaluate such water-related exposure routes as inhalation and dermal absorption when addressing microbial health effects. The nature and significance of other than the classical waterborne pathogens are to some degree tied to the particular type of waste sources.

- A new set of indicator organisms may need to be developed for tropical water if it is proven that the current fecal indicators can maintain viable cell populations in the soil and water for significant periods of time in uniform tropical conditions. Some potential alternative indicators to be fully explored are coliphage, other bacteriophage, and *Clostridium perfringens*.

- Because animal sources of pathogens of concern for human infection such as *Giardia lamblia*, *Cryptosporidium parvum*, and *Escherichia coli* 0157:H7 may be waterborne or washed into water and thus become a potential source for infection, they should not be ignored in risk assessment. A likely approach would be phylogenetic differentiation; that is, indicators that are specific to, or can discriminate among, animal sources.

- EPA intends to develop additional data on secondary infection routes and infection rates from prospective epidemiology studies and outbreaks from various types of exposure (e.g., shellfish consumption, drinking water, recreational exposure).

- EPA needs to improve sampling strategies for recreational water monitoring including consideration of rainfall and pollution events to trigger sampling.

2.6 RISK CHARACTERIZATION CONSIDERATIONS

On March 21, 1995, EPA's Administrator issued the *EPA Risk Characterization Policy and Guidance* (USEPA, 1995). This policy and guidance is intended to ensure that characterization information from each stage of a risk assessment is used in forming conclusions about risk and that this information is communicated from risk assessors to risk managers, and from EPA to the public. The policy also provides the basis for greater clarity, transparency, reasonableness, and consistency in risk assessments across EPA programs. The fundamental principles which form the basis for a risk characterization are as follows:

- Risk assessments should be transparent, in that the conclusions drawn from the science are identified separately from policy judgments, and the use of default values or methods and the use of assumptions in the risk assessment are clearly articulated.

- Risk characterizations should include a summary of the key issues and conclusions of each of the other components of the risk assessments, as well as describe the likelihood of harm. The summary should include a description of the overall strengths and limitations (including uncertainties) of the assessment and conclusions.

- Risk characterizations should be consistent in general format, but recognize the unique characteristics of each specific situation.

- Risk characterizations should include, at least in a qualitative sense, a discussion of how a specific risk and its context compares with similar risks. This may be accomplished by comparisons with other pollutants or situations on which the Agency has decided to act, or other situations with which the public may be familiar. The discussion should highlight the limitations of such comparisons.

- Risk characterization is a key component of risk communication, which is an interactive process involving exchange of information and expert opinion among individuals, groups, and institutions.

Additional guiding principles include:

- The risk characterization integrates the information from the hazard identification, dose-response, and exposure assessments, using a combination of qualitative information, quantitative information, and information regarding uncertainties.

- The risk characterization includes a discussion of uncertainty and variability in the risk assessment.

- Well-balanced risk characterizations present conclusions and information regarding the strengths and limitations of the assessment for other risk assessors, EPA decision-makers, and the public.

In developing the methodology presented here, EPA has closely followed the risk characterization guiding principles listed above. As States and Tribes adopt criteria using the 2000 Human Health Methodology, they are strongly encouraged to follow EPA's risk characterization guidance. There are a number of areas within the Methodology and criteria development process where risk characterization principles apply:

- Integration of cancer and noncancer assessments with exposure assessments, including bioaccumulation potential determinations, in essence, weighing the strengths and weaknesses of the risk assessment as a whole when developing a criterion.

- Selecting a fish consumption rate, either locally derived or the national default value, within the context of a target population (e.g., sensitive subpopulations) as compared to the general population.

- Presenting cancer and/or noncancer risk assessment options.

- Describing the uncertainty and variability in the hazard identification, the dose-response, and the exposure assessment.

2.7 DISCUSSION OF UNCERTAINTY

2.7.1 Observed Range of Toxicity Versus Range of Environmental Exposure

When characterizing a risk assessment, an important distinction to make is between the observed range of adverse effects (from an epidemiology or animal study) and the environmentally observed range of exposure (or anticipated human exposure) to the contaminant. In many cases, EPA intends to apply default factors to account for uncertainties or incomplete knowledge in developing RfDs or cancer risk assessments using nonlinear low-dose extrapolation to provide a margin of protection. In reality, the actual effect level and the environmental exposure levels may be separated by several orders of magnitude. The difference between the dose causing some observed response and the anticipated human exposure should be described by risk assessors and managers, especially when comparing criteria to environmental levels of a contaminant.

2.7.2 Continuum of Preferred Data/Use of Defaults

In both toxicological and exposure assessments, EPA has defined a continuum of preferred data for toxicological assessments ranging from a highest preference for chronic human data (e.g., studies that examine a long-term exposure of humans to a chemical, usually from occupational and/or residential exposure) and actual field data for many of the exposure parameter values (e.g., locally derived fish consumption rates, waterbody-specific bioaccumulation rates), to default values which are at the lower end of the preference continuum. EPA has supplied default values for all of the risk assessment parameters in the 2000 Human Health Methodology; however, it is important to note that when default values are used, the uncertainty in the final risk assessment may be higher, and the final resulting criterion may not be as applicable to local conditions, than is a risk assessment derived from human/field data. Using defaults assumes generalized conditions and may not capture the actual variability in the population (e.g., sensitive subpopulations/high-end consumers). If defaults are chosen as the basis for criteria, these inherent uncertainties should be communicated to the risk manager and the public. While this continuum is an expression of preference on the part of EPA, it does not imply in any way that any of the choices are unacceptable or scientifically indefensible.

2.7.3 Significant Figures

The number of significant figures in a numeric value is the number of certain digits plus one estimated digit. Digits should not be confused with decimal places. For example, 15.1, 0.0151, and 0.0150 all have 3 significant figures. Decimal places may have been used to maintain the correct number of significant figures, but in themselves they do not indicate significant figures (Brinker, 1984). Since the number of significant figures must include only one estimated digit, the sources of input parameters (e.g., fish consumption and water consumption rates) should be checked to determine the number of significant figures associated with data they provide. However, the original measured values may not be available to determine the number of significant figures in the input parameters. In these situations, EPA recommends utilizing the data as presented.

When developing criteria, EPA recommends rounding the number of significant figures at the end of the criterion calculation to the same number of significant figures in the least precise parameter. This is a generally accepted practice which can be found described in greater detail in APHA (1992) and Brinker (1984). The general rule is that for multiplication or division, the resulting value should not possess any more significant figures than is associated with the factor in the calculation with the least precision. When numbers are added or subtracted, the number that has the fewest decimal places, not necessarily the fewest significant figures, puts the limit on the number of places that justifiably may be carried in the sum or difference. Rounding off a number is the process of dropping one or more digits so that the value contains only those digits that are significant or necessary in subsequent computations (Brinker, 1984). The following rounding procedures are recommended: (1) if the digit 6, 7, 8, or 9 is dropped, increase the preceding digit by one unit; (2) if the digit 0, 1, 2, 3, or 4 is dropped, do not alter the preceding digit; and (3) if the digit 5 is dropped, round off the preceding digit to the nearest even number (e.g., 2.25 becomes 2.2 and 2.35 becomes 2.4) (APHA, 1992; Brinker, 1984).

EPA recommends that calculations of water quality criteria be performed without rounding of intermediate step values. The resulting criterion may be rounded to a manageable number of decimal places. However, in no case should the number of digits presented exceed the number of significant figures implied in the data and calculations performed on them. The term "intermediate step values" refers to values of the parameters in Equations 1-1 through 1-3. The final step is considered the resulting AWQC. Although AWQC are, in turn, used for purposes of establishing water quality-based effluent limits (WQBELs) in National Pollutant Discharge Elimination System (NPDES) permits, calculating total maximum daily loads (TMDLs), and applicable or relevant and appropriate requirements (ARARs) for Superfund, they are considered the final step of this Methodology and, for the purpose of this discussion, where the rounding should occur.

The determination of appropriate significant figures inevitably involves some judgment given that some of the equation parameters are adopted default exposure values. Specifically, the default drinking water intake rate of 2 L/day is a value adopted to represent a majority of the population over the course of a lifetime. Although supported by drinking water consumption survey data, this value was adopted as a policy decision and, as such, does not have to be considered in determining the parameter with the least precision. That is, the resulting AWQC need not always be reduced to one significant digit. Similarly, the 70-kg adult body weight has been adopted Agency-wide and represents a default policy decision.

The following example with a simplified AWQC equation illustrates the rule described above. The example is for hexachlorobutadiene (HCBD), which EPA used to demonstrate the 1998 draft Methodology revisions (USEPA, 1998b). The parameters that were calculated (i.e., not policy adopted values) include values with significant figures of two (the POD and RSC), three (the UF), and four (the FI and BAF). Based on the 2000 Human Health Methodology, the final criterion should be rounded to two significant figures. The bold numbers in parentheses indicate the number of significant figures and those with asterisks also indicate Agency adopted policy values.

$$AWQC = \frac{POD}{UF} \cdot RSC \cdot \left(\frac{BW}{DI + (FI \cdot BAF)} \right) \qquad \text{(Equation 2-1)}$$

Example [Refer to draft HCBD document for details on the POD/UF, RSC and BAF data (EPA 822-R-98-004). Also note that the fish intake rate in this example is the revised value.]:

$$AWQC = \left(\frac{0.054\mathbf{(2)}}{300\mathbf{(3)}} - 1.2 \times 10^{-4}\mathbf{(2)} \right) \times \left(\frac{70\mathbf{(2^{*})}}{2\mathbf{(1^{*})} + (0.01750\mathbf{(4)} \times 3{,}180\mathbf{(4)})} \right)$$

AWQC = 7.3×10^{-5} mg/L (0.073 µg/L, rounded from 7.285×10^{-2} µg/L)
* represents Agency adopted policy value

A number of the values used in the equation may result in intermediate step values that have more than four figures past the decimal place and may be carried throughout the calculation. However, carrying more than four figures past the decimal place (equivalent to the most precise parameter) is unnecessary as it has no effect on the resulting criterion value.

2.8 OTHER CONSIDERATIONS

2.8.1 Minimum Data Considerations

For many of the preceding technical areas, considerations have been presented for data quality in developing toxicological and exposure assessments. For greater detail and discussion of minimum data recommendations, the reader is referred to the specific sections in the Methodology on cancer and noncancer risk assessments (and especially to the referenced EPA risk assessment guidelines documents), exposure assessment, and bioaccumulation assessment, in addition to the TSD volumes for each.

2.8.2 Site-Specific Criterion Calculation

The 2000 Human Health Methodology allows for site-specific modifications by States and Tribes to reflect local environmental conditions and human exposure patterns. "Local" may refer to any appropriate geographic area where common aquatic environmental or exposure patterns exist. Thus "local" may signify Statewide, regional, a river reach, or an entire river.

Such site-specific criteria may be developed as long as the site-specific data, either toxicological or exposure-related, is justifiable. For example, when using a site-specific fish consumption rate, a State should use a value that represents at least the central tendency of the population surveyed (either sport or subsistence, or both). If a site-specific fish consumption rate for sport anglers or subsistence anglers is lower than an EPA default value, it may be used in calculating AWQC. However, to justify such a level (either higher or lower than EPA defaults), the State should assemble appropriate survey data to arrive at a defensible site-specific fish consumption rate.

Such data must also be submitted to EPA for its review when approving or disapproving State or Tribal water quality standards under Section 303(c). The same conditions apply to site-specific calculations of BAF, percent fish lipid, or the RSC. In the case of deviations from toxicological values (i.e., IRIS values: verified noncancer and cancer assessments), EPA strongly recommends that the data upon which the deviation is based be presented to and approved by the Agency before a criterion is developed.

Additional guidance on site-specific modifications to the 2000 Human Health Methodology is provided in each of the three TSD volumes.

2.8.3 Organoleptic Criteria

Organoleptic criteria define concentrations of chemicals or materials which impart undesirable taste and/or odor to water. Organoleptic effects, while significant from an aesthetic standpoint, are not a significant health concern. In developing and utilizing such criteria, two factors must be appreciated: (1) the limitations of most organoleptic data; and (2) the human health significance of organoleptic properties. In the past, EPA has developed organoleptic criteria if organoleptic data were available for a specific contaminant. The 1980 AWQC National Guidelines made a clear distinction that organoleptic criteria and toxicity-based criteria are derived from completely different endpoints, and that organoleptic criteria have no demonstrated relationship to potential adverse human health effects because there is no toxicological basis. EPA acknowledges that if organoleptic effects (i.e., objectionable taste and odor) cause people to reject the water and its designated uses, then the public is effectively deprived of the natural resource. It is also possible that intense organoleptic characteristics could result in depressed fluid intake which, in turn, might lead to an indirect human health effect via decreased fluid consumption. Although EPA has developed organoleptic criteria in the past and may potentially do so in the future, this will not be a significant part of the water quality criteria program. EPA encourages the development of organoleptic criteria when States and Tribes believe they are needed. However, EPA cautions States and Tribes that the quality of organoleptic data is often significantly less than that of toxicologic data used in establishing health-based criteria. Therefore, a comprehensive evaluation of available organoleptic data should be made, and the selection of the most appropriate database for the criterion should be based on sound scientific judgment.

In 1980, EPA provided recommended criteria summary language when both types of data are available. The following format was used and is repeated here:

> *For comparison purposes, two approaches were used to derive criterion levels for ____. Based on available toxicity data, for the protection of public health the derived level is ____. Using available organoleptic data, for controlling undesirable taste and odor quality of ambient water the estimated level is ____. It should be recognized that organoleptic data as a basis for establishing a water quality criteria have no demonstrated relationship to potential adverse human health effects.*

Similarly, the 1980 Methodology recommended that in those instances where a level to limit toxicity cannot be derived, the following statement should be provided:

> *Sufficient data are not available for ____ to derive a level which would protect against the potential toxicity of this compound.*

2.8.4 Criteria for Chemical Classes

The 2000 Human Health Methodology also allows for the development of a criterion for classes of chemicals, as long as a justification is provided through the analysis of mechanistic data, toxicokinetic data, structure-activity relationship data, and limited acute and chronic toxicity data. When potency differences between members of a class is great (such as in the case

of chlorinated dioxins and furans), toxicity equivalency factors (TEFs) may be more appropriately developed than one class criterion.

A chemical class is defined as any group of chemical compounds which are similar in chemical structure and biological activity, and which frequently occur together in the environment usually because they are generated by the same commercial process. In criterion development, isomers should be regarded as part of a chemical class rather than as a single compound. A class criterion, therefore, is an estimate of risk/safety which applies to more than one member of a class. It involves the use of available data on one or more chemicals of a class to derive criteria for other compounds of the same class in the event that there are insufficient data available to derive compound-specific criteria. The health-based criterion may apply to the water concentration of each member of the class, or may apply to the sum of the water concentrations of the compounds within the class. Because relatively minor structural changes within the class of compounds can have pronounced effects on their biological activities, reliance on class criteria should be minimized depending on the data available.

The following guidance should also be followed when considering the development of a class criterion.

- A detailed review of the chemical and physical properties of the chemicals within the group should be made. A close relationship within the class with respect to chemical activity would suggest a similar potential to reach common biological sites within tissues. Likewise, similar lipid solubilities would suggest the possibility of comparable absorption and distribution.

- Qualitative and quantitative toxicological data for chemicals within the group should be examined. Adequate toxicological data on a number of compounds within a group provides a more reasonable basis for extrapolation to other chemicals of the same class than minimal data on one chemical or a few chemicals within the group.

- Similarities in the nature of the toxicological response to chemicals in the class provides additional support for the prediction that the response to other members of the class may be similar. In contrast, where the biological response has been shown to differ markedly on a qualitative and quantitative basis for chemicals within a class, the extrapolation of a criterion to other members is not appropriate.

- Additional support for the validity of extrapolation of a criterion to other members of a class could be provided by evidence of similar metabolic and toxicokinetic data for some members of the class.

Additional guidance is described in the *Technical Support Document on Health Risk Assessment of Chemical Mixtures* (USEPA, 1990).

2.9.5 Criteria for Essential Elements

Developing criteria for essential elements, particularly metals, must be a balancing act between toxicity and the requirement for good health. The AWQC must consider essentiality and cannot be established at levels that would result in deficiency of the element in the human population. The difference between the recommended daily allowance (RDA) and the daily doses causing a specified risk level for carcinogens or the RfDs for noncarcinogens defines the spread of daily doses within which the criterion may be derived. Because errors are inherent in defining both essential and adverse-effect levels, the criterion is derived from a dose level near the center of such dose ranges.

The process for developing criteria for essential elements should be similar to that used for any other chemical with minor modifications. The RfD represents concern for one end of the exposure spectrum (toxicity), whereas the RDA represents the other end (minimum essentiality). While the RDA and RfD values might occasionally appear to be similar in magnitude to one another, it does not imply incompatibility of the two methodological approaches, nor does it imply inaccuracy or error in either calculation.

2.9 REFERENCES

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3. RISK ASSESSMENT

This section describes the methods used to estimate ambient water quality criteria (AWQC) for the protection of human health for carcinogenic chemicals (Section 3.1) and for noncarcinogenic chemicals (Section 3.2).

3.1 CANCER EFFECTS

3.1.1 Background on EPA Cancer Risk Assessment Guidelines

The current EPA *Guidelines for Carcinogen Risk Assessment* were published in 1986 (USEPA, 1986a, hereafter the "1986 cancer guidelines"). The 1986 cancer guidelines categorize chemicals into alpha-numerical Groups: A, known human carcinogen (sufficient evidence from epidemiological studies or other human studies); B, probable human carcinogen (sufficient evidence in animals and limited or inadequate evidence in humans); C, possible human carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); D, not classifiable (inadequate or no animal evidence of carcinogenicity); and E, evidence of noncarcinogenicity for humans (no evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiological and animal studies). Within Group B there are two subgroups, Groups B1 and B2. Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiological studies. Group B2 is generally for agents for which there is sufficient evidence from animal studies and for which there is inadequate evidence or no data from epidemiological studies (USEPA, 1986). The system was similar to that used by the International Agency for Research on Cancer (IARC).

The 1986 cancer guidelines include guidance on what constitutes sufficient, limited, or inadequate evidence. In epidemiological studies, sufficient evidence indicates a causal relationship between the agent and human cancer; limited evidence indicates that a causal relationship is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded; inadequate evidence indicates either lack of pertinent data, or a causal interpretation is not credible. In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association. In animal studies, sufficient evidence includes an increased incidence of malignant tumors or combined malignant and benign tumors:

- In multiple species or strains;
- In multiple experiments (e.g., with different routes of administration or using different dose levels);
- To an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset;
- Additional data on dose-response, short-term tests, or structural activity relationships.

In the 1986 cancer guidelines, hazard identification and the weight-of-evidence process focus on tumor findings. The weight-of-evidence approach for making judgments about cancer hazard analyzes human and animal tumor data separately, then combines them to make the overall conclusion about potential human carcinogenicity. The next step of the hazard analysis is an evaluation of supporting evidence (e.g., mutagenicity, cell transformation) to determine whether the overall weight-of-evidence conclusion should be modified.

For cancer risk quantification, the 1986 cancer guidelines recommend the use of linearized multistage model (LMS) as the only default approach. The 1986 cancer guidelines also mention that a low-dose extrapolation model other than the LMS might be considered more appropriate based on biological grounds. However, no guidance is given in choosing other approaches. The 1986 cancer guidelines recommended the use of body weight raised to the 2/3 power ($BW^{2/3}$) as a dose scaling factor between species.

3.1.2 EPA's Proposed Guidelines for Carcinogen Risk Assessment and the Subsequent July, 1999 Draft Revised Cancer Guidelines

In 1996, EPA published *Proposed Guidelines for Carcinogen Risk Assessment* (USEPA, 1996a, hereafter the "1996 proposed cancer guidelines"). After the publication of the 1996 proposed cancer guidelines and a February, 1997 and January, 1999 Science Advisory Board (SAB) review, a revision was made in July, 1999 *Guidelines for Carcinogen Risk Assessment - Review Draft* (hereafter the "1999 draft revised cancer guidelines"; USEPA, 1999a), and an SAB meeting was convened to review this revised document. When final guidelines are published, they will replace the 1986 cancer guidelines. These revisions are designed to ensure that the Agency's cancer risk assessment methods reflect the most current scientific information and advances in risk assessment methodology.

In the meanwhile, the 1986 guidelines are used and extended with principles discussed in the 1999 draft revised cancer guidelines. These principles arise from scientific discoveries concerning cancer made in the last 15 years and from EPA policy of recent years supporting full characterization of hazard and risk both for the general population and potentially sensitive groups such as children. These principles are incorporated in recent and ongoing assessments such as the reassessment of dioxin, consistent with the 1986 guidelines. Until final guidelines are published, information is presented to describe risk under both the 1986 guidelines and 1999 draft revisions.

The 1999 draft revised cancer guidelines call for the full use of all relevant information to convey the circumstances or conditions under which a particular hazard is expressed (e.g., route, duration, pattern, or magnitude of exposure). They emphasize understanding the mode of action (MOA) whereby the agent induces tumors. The MOA underlies the hazard assessment and provides the rationale for dose-response assessments.

The key principles in the 1999 draft revised cancer guidelines include:

a) Hazard assessment is based on the analysis of all biological information rather than just tumor findings.

b) An agent's MOA in causing tumors is emphasized to reduce the uncertainty in describing the likelihood of harm and in determining the dose-response approach(es).

c) The 1999 draft revised cancer guidelines emphasize the conditions under which the hazard may be expressed (e.g., route, pattern, duration and magnitude of exposure). Further, the guidelines call for a *hazard characterization* to integrate the data analysis of all relevant studies into a weight-of-evidence conclusion of hazard and to develop a working conclusion regarding the agent's mode of action in leading to tumor development.

d) A weight-of-evidence narrative with accompanying descriptors (listed in Section 3.1.3.1 below) would replace the current alphanumeric classification system. The narrative summarizes the key evidence for carcinogenicity, describes the agent's MOA, characterizes the conditions of hazard expression, including route of exposure, describes any disproportionate effects on subgroups of the human population (e.g., children), and recommends appropriate dose-response approach(es). Significant strengths, weaknesses, and uncertainties of contributing evidence are also highlighted.

e) Biologically based extrapolation models are the preferred approach for quantifying risk. These models integrate data and conclusions about events in the carcinogenic process throughout the dose-response range from high to low doses. It is anticipated, however, that the necessary data for the parameters used in such models will not be available for most chemicals. The 1999 draft revised cancer guidelines allow for alternative quantitative methods, including several default approaches.

f) Dose-response assessment is a two-step process. In the first step, response data are modeled in the observable range of data and a determination is made of the point of departure (POD) from the observed range to extrapolate to low doses. The second step is extrapolation from the POD to estimate dose-response at lower doses. In addition to modeling tumor data, the 1999 draft revised cancer guidelines call for the use and modeling of other kinds of responses if they are considered to be more informed measures of carcinogenic risk. Nominally, these responses reflect key events in the carcinogenic process integral to the MOA of the agent.

g) Three default approaches are provided–linear, nonlinear, or both when adequate data are unavailable to generate a biologically based model. As the first step for all approaches, curve fitting in the observed range is used to determine a POD. A standard POD is the effective dose corresponding to the lower 95 percent limit on

a dose associated with 10 percent extra risk (LED_{10}).[3] *Linear*: The linear default is a straight line extrapolation from the response at LED_{10} to the origin (zero dose, zero extra risk). *Nonlinear*: The nonlinear default begins with the identified POD and provides a margin of exposure (MOE) analysis rather than estimating the probability of effects at low doses. The MOE analysis is used to determine the appropriate margin between the POD and the exposure level of interest, in this Methodology, the AWQC. The key objective of the MOE analysis is to describe for the risk manager how rapidly responses may decline with dose. Other factors are also considered in the MOE analysis (i.e., nature of the response, slope of the dose-response curve, human sensitivity compared with experimental animals, nature and extent of human variability in sensitivity and human exposure). *Linear and nonlinear*: Section 3.1.3.4E describes the situations when both linear and nonlinear defaults are used.

h) The approach used to calculate an oral human equivalent dose when assessments are based on animal bioassays has been refined and includes a change in the default assumption for interspecies dose scaling. The 1999 draft revised cancer guidelines use body weight raised to the 3/4 power.

EPA health risk assessment practices for both cancer and noncancer endpoints are beginning to come together with recent proposals to emphasize MOA understanding in risk assessment and to model response data in the observable range to derive PODs for data sets and benchmark doses (BMDs) for individual studies. The modeling of observed response data to identify PODs in a standard way will help to harmonize cancer and noncancer dose-response approaches and permit comparisons of cancer and noncancer risk estimates.

3.1.3 Methodology for Deriving AWQC[4] by the 1999 Draft Revised Cancer Guidelines

Following the publication of the *Draft Water Quality Criteria Methodology: Human Health* (USEPA, 1998a) and the accompanying TSD (USEPA, 1998b), EPA received comments from the public. EPA also held an external peer review of the draft Methodology. Both the peer reviewers and the public recommended that EPA incorporate the new approaches into the AWQC Methodology.

Until new guidelines are published, the 1986 cancer guidelines will be used along with principles of the 1999 draft revised cancer guidelines. The 1986 guidelines are the basis for IRIS risk numbers which were used to derive the current AWQC. Each new assessment applying the principles of the 1999 draft revised cancer guidelines will be subject to peer review before being used as the basis of AWQC.

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[3] Use of the LED_{10} as the point of departure is recommended with this Methodology, as it is with the 1999 draft revised cancer guidelines.

[4] Additional information regarding the revised method for assessing carcinogens may be found in the *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000). Technical Support Document, Volume 1: Risk Assessment* (USEPA, 2000).

The remainder of Section 3 illustrates the methodology for deriving numerical AWQC for carcinogens applying the 1999 draft revised cancer guidelines (USEPA, 1999a). This discussion of the revised methodology for carcinogens focuses primarily on the quantitative aspects of deriving numerical AWQC values. It is important to note that the cancer risk assessment process outlined in the 1999 draft revised cancer guidelines is not limited to the quantitative aspects. A numerical AWQC value derived for a carcinogen is to be based on appropriate hazard characterization and accompanied by risk characterization information.

This section contains a discussion of the weight-of-evidence narrative, that describes all information relevant to a cancer risk evaluation, followed by a discussion of the quantitative aspects of deriving numerical AWQC values for carcinogens. It is assumed that data from an appropriately conducted animal bioassay or human epidemiological study provide the underlying basis for deriving the AWQC value. The discussion focuses on the following: (1) the weight-of-evidence narrative; (2) general considerations and framework for analysis of the MOA; (3) dose estimation; (4) characterizing dose-response relationships in the range of observation and at low, environmentally relevant doses; (5) calculating the AWQC value; (6) risk characterization; and (7) use of Toxicity Equivalent Factors (TEF) and Relative Potency Estimates. The first three topics encompass the quantitative aspects of deriving AWQC for carcinogens.

3.1.3.1 Weight-of-Evidence Narrative[5]

The 1999 draft revised cancer guidelines include a weight-of-evidence narrative that is based on an overall judgment of biological and chemical/physical considerations. Hazard assessment information accompanying an AWQC value for a carcinogen in the form of a weight-of-evidence narrative is described in the footnote. Of particular importance is that the weight-of-evidence narrative explicitly provides adequate support based on human studies, animal bioassays, and other key evidence for the conclusion whether the substance is or is likely to be carcinogenic to humans from exposures through drinking water and/or fish ingestion. The Agency emphasizes the importance of providing an explicit discussion of the MOA for the substance in the weight-of-evidence narrative if data are available, including a discussion that relates the MOA to the quantitative procedures used in the derivation of the AWQC.

3.1.3.2 Mode of Action - General Considerations and Framework for Analysis

[5] The weight-of-evidence narrative is intended for the risk manager, and thus explains in nontechnical language the key data and conclusions, as well as the conditions for hazard expression. Conclusions about potential human carcinogenicity are presented by route of exposure. Contained within this narrative are simple likelihood descriptors that essentially distinguish whether there is enough evidence to make a projection about human hazard (i.e., Carcinogenic to humans; Likely to be carcinogenic to humans; Suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential; Data are inadequate for an assessment of human carcinogenic potential; and Not likely to be carcinogenic to humans). Because one encounters a variety of data sets on agents, these descriptors are not meant to stand alone; rather, the context of the weight-of-evidence narrative is intended to provide a transparent explanation of the biological evidence and how the conclusions were derived. Moreover, these descriptors should not be viewed as classification categories (like the alphameric system), which often obscure key scientific differences among chemicals. The new weight-of-evidence narrative also presents conclusions about how the agent induces tumors and the relevance of the mode of action to humans, and recommends a dose-response approach based on the MOA understanding (USEPA, 1996a, 1999a).

An MOA is composed of key events and processes starting with the interaction of an agent with a cell, through operational and anatomical changes, resulting in cancer formation. "Mode" of action is contrasted with "mechanism" of action, which implies a more detailed, molecular description of events than is meant by MOA.

Mode of action analysis is based on physical, chemical, and biological information that helps to explain key events[6] in an agent's influence on development of tumors. Inputs to MOA analysis include tumor data in humans, animals, and among structural analogues as well as the other key data.

There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression. All pertinent studies are reviewed in analyzing an MOA, and an overall weighing of evidence is performed, laying out the strengths, weaknesses, and uncertainties of the case as well as potential alternative positions and rationales. Identifying data gaps and research needs is also part of the assessment.

Mode of action conclusions are used to address the question of human relevance of animal tumor responses, to address differences in anticipated response among humans such as between children and adults or men and women, and as the basis of decisions about the anticipated shape of the dose-response relationship.

In reaching conclusions, the question of "general acceptance" of an MOA will be tested as part of the independent peer review that EPA obtains for its assessment and conclusions.

Framework for Evaluating a Postulated Carcinogenic Mode(s) of Action

The framework is intended to be an analytic tool for judging whether available data support a mode of carcinogenic action postulated for an agent and includes nine elements:

1. Summary description of postulated MOA
2. Identification of key events
3. Strength, consistency, specificity of association
4. Dose-response relationship
5. Temporal relationship
6. Biological plausibility and coherence
7. Other modes of action
8. Conclusion
9. Human relevance, including subpopulations

3.1.3.3 Dose Estimation

[6]A "key event" is an empirically observable, precursor step that is itself a necessary element of the mode of action, or is a marker for such an element.

A. Determining the Human Equivalent Dose by the Oral Route

An important objective in the dose-response assessment is to use a measure of internal or delivered dose at the target site where possible. This is particularly important in those cases where the carcinogenic response information is being extrapolated to humans from animal studies. Generally, by the oral exposure route, the measure of a dose provided in the underlying human studies or animal bioassays is the applied dose, typically given in terms of unit mass per unit body weight per unit time, (e.g., mg/kg-day). When animal bioassay data are used, it is necessary to make adjustments to the applied dose values to account for differences in toxicokinetics between animals and humans that affect the relationship between applied dose and delivered dose at the target organ.

In the estimation of a human equivalent dose, the 1999 draft revised cancer guidelines recommend that when adequate data are available, the doses used in animal studies can be adjusted to equivalent human doses using toxicokinetic information on the particular agent. However, in most cases, there are insufficient data available to compare dose between species. In these cases, the estimate of a human equivalent dose is based on science policy default assumptions. To derive an equivalent human oral dose from animal data, the default procedure in the 1999 draft revised cancer guidelines is to scale daily applied oral doses experienced for a lifetime in proportion to body weight raised to the 3/4 power ($BW^{3/4}$). The adjustment factor is used because metabolic rates, as well as most rates of physiological processes that determine the disposition of dose, scale this way. Thus, the rationale for this factor rests on the empirical observation that rates of physiological processes consistently tend to maintain proportionality with body weight raised to 3/4 power (USEPA, 1992a, 1999a).

The use of $BW^{3/4}$ is a departure from the scaling factor of $BW^{2/3}$ that was based on surface area adjustment and was included in the 1980 AWQC National Guidelines as well as the 1986 cancer guidelines.

B. Dose-Response Analysis

If data on the agent are sufficient to support the parameters of a biologically based model and the purpose of the assessment is such as to justify investing resources supporting its use, this is the preferred approach for both the observed tumor and related response data and for extrapolation below the range of observed data in either animal or human studies.

3.1.3.4 Characterizing Dose-Response Relationships in the Range of Observation and at Low Environmentally Relevant Doses

The first quantitative component in the derivation of AWQC for carcinogens is the dose-response assessment in the range of observation. For most agents, in the absence of adequate data to generate a biologically based model, dose-response relationships in the observed range can be addressed through curve-fitting procedures for response data. It should be noted that the 1999 draft revised cancer guidelines call for modeling of not only tumor data in the observable range, but also other responses thought to be important events preceding tumor development (e.g., DNA adducts, cellular proliferation, receptor binding, hormonal changes). The modeling of

these data is intended to better inform the dose-response assessment by providing insights into the relationships of exposure (or dose) below the observable range for tumor response. These non-tumor response data can only play a role in the dose-response assessment if the agent's carcinogenic mode of action is reasonably understood, as well as the role of that precursor event.

The 1999 draft revised cancer guidelines recommend calculating the lower 95 percent confidence limit on a dose associated with an estimated 10 percent increased tumor or relevant non-tumor response (LED_{10}) for quantitative modeling of dose-response relationships in the observed range. The estimate of the LED_{10} is used as the POD for low-dose extrapolations discussed below. This standard point of departure (LED_{10}) is adopted as a matter of science policy to remain as consistent and comparable from case to case as possible. It is also a convenient comparison point for noncancer endpoints. The rationale supporting use of the LED_{10} is that a 10 percent response is at or just below the limit of sensitivity for discerning a statistically significant tumor response in most long-term rodent studies and is within the observed range for other toxicity studies. Use of lower limit takes experimental variability and sample size into account. The ED_{10} (central estimate) is also presented as a reference for comparison uses, especially for use in relative hazard/potency ranking among agents for priority setting.

For some data sets, a choice of the POD other than the LED_{10} may be appropriate. The objective is to determine the lowest reliable part of the dose-response curve for the beginning of the second step of the dose-response assessment—determine the extrapolation range. Therefore, if the observed response is below the LED_{10}, then a lower point may be a better choice (e.g., LED_5). Human studies more often support a lower POD than animal studies because of greater sample size.

The POD may be a NOAEL when a margin of exposure analysis is the nonlinear dose-response approach. The kinds of data available and the circumstances of the assessment both contribute to deciding to use a NOAEL or LOAEL which is not as rigorous or as ideal as curve fitting, but can be appropriate. If several data sets for key events and tumor response are available for an agent, and they are a mixture of continuous and incidence data, the most practicable way to assess them together is often through a NOAEL/LOAEL approach.

When an LED value estimated from animal data is used as the POD, it is adjusted to the human equivalent dose using an interspecies dose adjustment or a toxicokinetic analysis as described in Section 3.1.3.3.

Analysis of human studies in the observed range is designed on a case-by-case basis depending on the type of study and how dose and response are measured in the study.

A. Extrapolation to Low, Environmentally Relevant Doses

In most cases, the derivation of an AWQC will require an evaluation of carcinogenic risk at environmental exposure levels substantially lower than those used in the underlying study. Various approaches are used to extrapolate risk outside the range of observed experimental data. In the 1999 draft revised cancer guidelines, the choice of extrapolation method is largely

dependent on the mode of action. It should be noted that the term "mode of action" (MOA) is deliberately chosen in the 1999 draft revised cancer guidelines in lieu of the term "mechanism" to indicate using knowledge that is sufficient to draw a reasonable working conclusion without having to know the processes in detail as the term mechanism might imply. The 1999 draft revised cancer guidelines favor the choice of a biologically based model, if the parameters of such models can be calculated from data sources independent of tumor data. It is anticipated that the necessary data for such parameters will not be available for most chemicals. Thus, the 1999 draft revised cancer guidelines allow for several default extrapolation approaches (low-dose linear, nonlinear, or both).

B. Biologically Based Modeling Approaches

If a biologically based approach has been used to characterize the dose-response relationships in the observed range, and the confidence in the model is high, it may be used to extrapolate the dose-response relationship to environmentally relevant doses. For the purposes of deriving AWQC, the environmentally relevant dose would be the risk-specific dose (RSD) associated with incremental lifetime cancer risks in the 10^{-6} to 10^{-4} range for carcinogens for which a linear extrapolation approach is applied.[7] The use of the RSD and the POD/UF to compute the AWQC is presented in Section 3.1.3.5, below. Although biologically-based approaches are appropriate both for characterizing observed dose-response relationships and extrapolating to environmentally relevant doses, it is not expected that adequate data will be available to support the use of such approaches for most substances. In the absence of such data, the default linear approach, the nonlinear (MOE) approach, or both linear and nonlinear approaches will be used.

[7] For discussion of the cancer risk range, see Section 2.4.

C. Default Linear Extrapolation Approach

The default linear approach replaces the LMS approach that has served as the default for EPA cancer risk assessments. Any of the following conclusions leads to selection of a linear dose-response assessment approach:

- There is an absence of sufficient tumor MOA information.
- The chemical has direct DNA mutagenic reactivity or other indications of DNA effects that are consistent with linearity.
- Human exposure or body burden is high and near doses associated with key events in the carcinogenic process (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin).
- Mode of action analysis does not support direct DNA effects, but the dose-response relationship is expected to be linear (e.g., certain receptor-mediated effects).

The procedures for implementing the default linear approach begin with the estimation of a POD as described above. The point of departure, LED_{10}, reflects the interspecies conversion to the human equivalent dose and the other adjustments for less-than-lifetime experimental duration. In most cases, the extrapolation for estimating response rates at low, environmentally relevant exposures is accomplished by drawing a straight line between the POD and the origin (i.e., zero dose, zero extra risk). This is mathematically represented as:

$$y = mx + b \qquad \text{(Equation 3-1)}$$
$$b = 0$$

where:

y	=	Response or incidence
m	=	Slope of the line (cancer potency factor) = $\triangle y/\triangle x$
x	=	Dose
b	=	Slope intercept

The slope of the line, "m" (the estimated cancer potency factor at low doses), is computed as:

$$m = \frac{0.10}{LED_{10}} \qquad \text{(Equation 3-2)}$$

The RSD is then calculated for a specific incremental targeted lifetime cancer risk (in the range of 10^{-6} to 10^{-4}) as:

$$RSD = \frac{\text{Target Incremental Cancer Risk}}{m} \qquad \text{(Equation 3-3)}$$

where:

RSD	=	Risk-specific dose (mg/kg-day)
Target Incremental Cancer Risk[8]	=	Value in the range of 10^{-6} to10^{-4}
m	=	Cancer potency factor $(mg/kg\text{-}day)^{-1}$

The use of the RSD to compute the AWQC is described in Section 3.1.3.5 below.

D. Default Nonlinear Approach

As discussed in the 1999 draft revised cancer guidelines, any of the following conclusions leads to a selection of a nonlinear (MOE) approach to dose-response assessment:

- A tumor MOA supporting nonlinearity applies (e.g., some cytotoxic and hormonal agents such as disruptors of hormonal homeostasis), and the chemical does not demonstrate mutagenic effects consistent with linearity.

- An MOA supporting nonlinearity has been demonstrated, and the chemical has some indication of mutagenic activity, but it is judged not to play a significant role in tumor causation.

Thus, a default assumption of nonlinearity is appropriate when there is no evidence for linearity and sufficient evidence to support an assumption of nonlinearity. The MOA may lead to a dose-response relationship that is nonlinear, with response falling much more quickly than linearly with dose, or being most influenced by individual differences in sensitivity. Alternatively, the MOA may theoretically have a threshold (e.g., the carcinogenicity may be a secondary effect of toxicity or of an induced physiological change that is itself a threshold phenomenon).

The nonlinear approach may be used, for instance, in the case of a bladder tumor inducer, where the chemical is not mutagenic and causes only stone formation in male rat bladders at high doses. This dynamic leads to tumor formation only at the high doses. Stone and subsequent tumor formation are not expected to occur at doses lower than those that induce the physiological changes that lead to stone formation. (More detail on this chemical is provided in the cancer section of the Risk Assessment TSD; USEPA, 2000). EPA does not generally try to distinguish between modes of action that might imply a "true threshold" from others with a

[8]In 1980, the target lifetime cancer risk range was set at 10-7 to 10-5. However, both the expert panel for the AWQC workshop (USEPA, 1993) and the peer review workshop experts (USEPA,1999c) recommended that EPA change the risk range to 10-6 to 10-4, to be consistent with SDWA program decisions. See Section 2.4 for more details.

nonlinear dose-response relationship, because there is usually not sufficient information to distinguish between those possibilities empirically.

The nonlinear MOE approach in the 1986 proposed cancer guidelines compares an observed response rate such as the LED_{10}, NOAEL, or LOAEL with actual or nominal environmental exposures of interest by computing the ratio between the two. In the context of deriving AWQC, the environmentally relevant exposures are nominal targets rather than actual exposures.

If the evidence for an agent indicates nonlinearity (e.g., when carcinogenicity is secondary to another toxicity for which there is a threshold), the MOE analysis for the toxicity is similar to what is done for a noncancer endpoint, and an RfD or RfC for that toxicity may also be estimated and considered in the cancer assessment. However, a threshold of carcinogenic response is not necessarily assumed. It should be noted that for cancer assessment, the MOE analysis begins from a POD that is adjusted for toxicokinetic differences between species to give a human equivalent dose.

To support the use of the MOE approach, risk assessment information provides evaluation of the current understanding of the phenomena that may be occurring as dose (exposure) decreases substantially below the observed data. This gives information about the risk reduction that is expected to accompany a lowering of exposure. The various factors that influence the selection of the UF in an MOE approach are also discussed below.

There are two main steps in the MOE approach. The first step is the selection of a POD. The POD may be the LED_{10} for tumor incidence or a precursor, or in some cases, it may also be appropriate to use a NOAEL or LOAEL value. When animal data are used, the POD is a human equivalent dose or concentration arrived at by interspecies dose adjustment (as discussed in Section 3.1.3.3) or toxicokinetic analysis.

The second step in using MOE analysis to establish AWQC is the selection of an appropriate margin or UF to apply to the POD. This is supported by analyses in the MOE discussion in the risk assessment. The following issues should be considered when establishing the overall UF for the derivation of AWQC using the MOE approach (others may be found appropriate in specific cases):

- The nature of the response used for the dose-response assessment, for instance, whether it is a precursor effect or a tumor response. The latter may support a greater MOE.

- The slope of the observed dose-response relationship at the POD and its uncertainties and implications for risk reduction associated with exposure reduction. (A steeper slope implies a greater reduction in risk as exposure decreases. This may support a smaller MOE).

- Human sensitivity compared with that of experimental animals.

- Nature and extent of human variability and sensitivity.

- Human exposure. The MOE evaluation also takes into account the magnitude, frequency, and duration of exposure. If the population exposed in a particular scenario is wholly or largely composed of a subpopulation of special concern (e.g., children) for whom evidence indicates a special sensitivity to the agent's MOA, an adequate MOE would be larger than for general population exposure.

E. Both Linear and Nonlinear Approaches

Any of the following conclusions leads to selection of both a linear and nonlinear approach to dose-response assessment. Relative support for each dose-response method and advice on the use of that information needs to be documented for the AWQC. In some cases, evidence for one MOA is stronger than for the other, allowing emphasis to be placed on that dose-response approach. In other cases, both modes of action are equally possible, and both dose-response approaches should be emphasized.

- Modes of action for a single tumor type support both linear and nonlinear dose response in different parts of the dose-response curve (e.g., 4,4' methylene chloride).

- A tumor mode of action supports different approaches at high and low doses; e.g., at high dose, nonlinearity, but, at low dose, linearity (e.g., formaldehyde).

- The agent is not DNA-reactive and all plausible modes of action are consistent with nonlinearity, but not fully established.

- Modes of action for different tumor types support differing approaches, e.g., nonlinear for one tumor type and linear for another due to lack of MOA information (e.g., trichloroethylene).

3.1.3.5 AWQC Calculation

A. Linear Approach

The following equation is used for the calculation of the AWQC for carcinogens where an RSD is obtained from the linear approach:

$$AWQC = RSD \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right) \qquad \text{(Equation 3-4)}$$

AWQC	=	Ambient water quality criterion (mg/L)
RSD	=	Risk-specific dose (mg/kg-day)
BW	=	Human body weight (kg)
DI	=	Drinking water intake (L/day)

FI_i	=	Fish intake at trophic level I (I = 2, 3, and 4) (kg/day)
BAF_i	=	Bioaccumulation factor for trophic level I (I = 2, 3, and 4), lipid normalized (L/kg)

B. Nonlinear Approach

In those cases where the nonlinear, MOE approach is used, a similar equation is used to calculate the AWQC [9]

$$AWQC = \frac{POD}{UF} \cdot RSC \cdot \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \cdot BAF_i)} \right) \qquad \text{(Equation 3-5)}$$

where variables are defined as for Equation 3-4 and:

POD	=	Point of departure (mg/kg-day)
UF	=	Uncertainty factor (unitless)
RSC	=	Relative source contribution (percentage or subtraction)

Differences between the AWQC values obtained using the linear and nonlinear approaches should be noted. First, the AWQC value obtained using the default linear approach corresponds to a specific estimated incremental lifetime cancer risk level in the range of 10^{-4} to 10^{-6}. In contrast, the AWQC obtained using the nonlinear approach does not describe a specific cancer risk. The AWQC calculations shown above are appropriate for waterbodies that are used as sources of drinking water.

The actual AWQC chosen for the protection of human health is based on a review of all relevant information, including cancer and noncancer data. The AWQC may, or may not, utilize the value obtained from the cancer analysis in the final AWQC value. The endpoint selected for the AWQC will be based on consideration of the weight of evidence and a complete analysis of all toxicity endpoints.

3.1.3.6 Risk Characterization

Risk assessment is an integrative process that is documented in a risk characterization summary. Risk characterization is the final step of the risk assessment process in which all preceding analyses (i.e., hazard, dose-response, and exposure assessments) are tied together to convey the overall conclusions about potential human risk. This component of the risk assessment process characterizes the data in nontechnical terms, explaining the extent and weight of evidence, major points of interpretation and rationale, and strengths and weaknesses of

[9] Although appearing in this equation as a factor to be multiplied, the RSC can also be an amount subtracted.

the evidence, and discussing alternative approaches, conclusions, uncertainties, and variability that deserve serious consideration.

Risk characterization information accompanies the numerical AWQC value and addresses the major strengths and weaknesses of the assessment arising from the availability of data and the current limits of understanding the process of cancer causation. Key issues relating to the confidence in the hazard assessment and the dose-response analysis (including the low-dose extrapolation procedure used) are discussed. Whenever more than one interpretation of the weight of evidence for carcinogenicity or the dose-response characterization can be supported, and when choosing among them is difficult, the alternative views are provided along with the rationale for the interpretation chosen in the derivation of the AWQC value. Where possible, quantitative uncertainty analyses of the data are provided; at a minimum, a qualitative discussion of the important uncertainties is presented.

3.1.3.7 Use of Toxicity Equivalence Factors and Relative Potency Estimates

The 1999 draft revised cancer guidelines state:

> *A toxicity equivalence factor (TEF) procedure is one used to derive quantitative dose-response estimates for agents that are members of a category or class of agents. TEFs are based on shared characteristics that can be used to order the class members by carcinogenic potency when cancer bioassay data are inadequate for this purpose. The ordering is by reference to the characteristics and potency of a well-studied member or members of the class. Other class members are indexed to the reference agent(s) by one or more shared characteristics to generate their TEFs.*

In addition, the 1999 draft revised cancer guidelines state that TEFs are generated and used for the limited purpose of assessment of agents or mixtures of agents in environmental media when better data are not available. When better data become available for an agent, the TEF should be replaced or revised. To date, adequate data to support use of TEFs have been found only for dibenzofurans (dioxins) and coplanar polychlorinated biphenyls (PCBs) (USEPA, 1989, 1999b).

The uncertainties associated with TEFs must be described when this approach is used. This is a default approach to be used when tumor data are not available for individual components in a mixture. Relative potency factors (RPFs) can be similarly derived and used for agents with carcinogenicity or other supporting data. The RPF is conceptually similar to TEFs, but does not have the same level of data to support it and thus has a less rigorous definition compared with the TEF. TEFs and RPFs are used only when there is no better alternative. When they are used, assumptions and uncertainties associated with them are discussed. As of today, there are only three classes of compounds for which relative potency approaches have been examined by EPA: dibenzofurans (dioxins), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs). There are limitations to the use of TEF and RFP approaches, and caution should be exercised when using them. More guidance can be found in the draft document for conducting health risk assessment of chemical mixtures, published by the EPA Risk Assessment Forum (USEPA,1999b).

3.1.4 References for Cancer Section

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3.2 NONCANCER EFFECTS

3.2.1 1980 AWQC National Guidelines for Noncancer Effects

In the 1980 AWQC National Guidelines, the Agency evaluated noncancer human health effects from exposure to chemical contaminants using Acceptable Daily Intake (ADI) levels. ADIs were calculated by dividing NOAELs by safety factors (SFs) to obtain estimates of doses of chemicals that would not be expected to cause adverse effects over a lifetime of exposure. In accordance with the National Research Council report of 1977 (NRC, 1977), EPA used SFs of 10, 100, or 1,000, depending on the quality and quantity of the overall database. In general, a factor of 10 was suggested when good-quality data identifying a NOAEL from human studies were available. A factor of 100 was suggested if no human data were available, but the database contained valid chronic animal data. For chemicals with no human data and scant animal data, a factor of 1,000 was recommended. Intermediate SFs could also be used for databases that fell between these categories.

AWQC were calculated using the ADI levels together with standard exposure assumptions about the rates of human ingestion of water and fish, and also accounting for intake from other sources (see Equation 1-1 in the Introduction). Surface water concentrations at or below the calculated criteria concentrations would be expected to result in human exposure levels at or below the ADI. Inherent in these calculations is the assumption that, generally, adverse effects from noncarcinogens exhibit a threshold.

3.2.2 Noncancer Risk Assessment Developments Since 1980

Since 1980, the risk assessment of noncarcinogenic chemicals has changed. To remove the value judgments implied by the words “acceptable” and “safety,” the ADI and SF terms have been replaced with the terms RfD and UF/modifying factor (MF), respectively.

For the risk assessment of general systemic toxicity, the Agency currently uses the guidelines contained in the IRIS background document entitled *Reference Dose (RfD): Description and Use in Health Risk Assessments* (hereafter the “IRIS background document”. That document defines an RfD as “an estimate (with uncertainty spanning approximately an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects over a lifetime” (USEPA,

1993a). The most common approach for deriving the RfD does not involve dose-response modeling. Instead, an RfD for a given chemical is usually derived by first identifying the NOAEL for the most sensitive known toxicity endpoint, that is, the toxic effect that occurs at the lowest dose. This effect is called the critical effect. Factors such as the study protocol, the species of experimental animal, the nature of the toxicity endpoint assessed and its relevance to human effects, the route of exposure, and exposure duration are critically evaluated in order to select the most appropriate NOAEL from among all available studies in the chemical's database. If no appropriate NOAEL can be identified from any study, then the LOAEL for the critical effect endpoint is used and an uncertainly factor for LOAEL-to-NOAEL extrapolation is applied. Using this approach, the RfD is equal to the NOAEL (or LOAEL) divided by the product of UFs and, occasionally, an MF:

$$\text{RfD (mg/kg/day)} = \frac{\text{NOAEL (or LOAEL)}}{\text{UF} \cdot \text{MF}} \qquad \text{(Equation 3-6)}$$

The definitions and guidance for use of the UFs and the MFs are provided in the IRIS background document and are repeated in Table 3-1.

The IRIS background document on the RfD (USEPA, 1993a) provides guidance for critically assessing noncarcinogenic effects of chemicals and for deriving the RfD. Another reference on this topic is Dourson (1994). Furthermore, the Agency has also published separate guidelines for assessing specific toxic endpoints, such as developmental toxicity (USEPA, 1991a), reproductive toxicity (USEPA, 1996a), and neurotoxicity risk assessment (USEPA, 1995). These endpoint-specific guidelines will be used for their respective areas in the hazard assessment step and will complement the overall toxicological assessment. It should be noted, however, that an RfD, derived using the most sensitive known endpoint, is considered protective against all noncarcinogenic effects.

TABLE 3-1. UNCERTAINTY FACTORS AND THE MODIFYING FACTOR

Uncertainty Factor	Definition
UF_H	Use a 1, 3, or 10-fold factor when extrapolating from valid data in studies using long-term exposure to average healthy humans. This factor is intended to account for the variation in sensitivity (intraspecies variation) among the members of the human population.
UF_A	Use an additional factor of 1, 3, or 10 when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans (interspecies variation).
UF_S	Use an additional factor of 1, 3, or 10 when extrapolating from less-than-chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less-than-chronic NOAELs to chronic NOAELs.
UF_L	Use an additional factor of 1, 3, or 10 when deriving an RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs.
UF_D	Use an additional 3- or 10-fold factor when deriving an RfD from an "incomplete" database. This factor is meant to account for the inability of any single type of study to consider all toxic endpoints. The intermediate factor of 3 (approximately ½ $\log_{10}$ unit, i.e., the square root of 10) is often used when there is a single data gap exclusive of chronic data. It is often designated as UF_D.

Modifying Factor

Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above (e.g., the number of species tested). The default value for the MF is 1.

Note: With each UF or MF assignment, it is recognized that professional scientific judgment must be used. The total product of the uncertainty factors and modifying factor should not exceed 3,000.

Similar to the procedure used in the 1980 AWQC National Guidelines, the revised method of deriving AWQC for noncarcinogens uses the RfD together with various assumptions concerning intake of the contaminant from both water and non-water sources of exposure. The objective of an AWQC for noncarcinogens is to ensure that human exposure to a substance related to its presence in surface water, combined with exposure from other sources, does not exceed the RfD. The algorithm for deriving AWQC for noncarcinogens using the RfD is presented as Equation 1-1 in the Introduction.

3.2.3 Issues and Recommendations Concerning the Derivation of AWQC for Noncarcinogens

During a review of the 1980 AWQC National Guidelines (USEPA, 1993b), the Agency identified several issues that must be resolved in order to develop a final revised methodology for deriving AWQC based on noncancer effects. These issues, as discussed below, mainly concern the derivation of the RfD as the basis for such an AWQC. Foremost among these issues is whether the Agency should revise the present method or adopt entirely new procedures that use quantitative dose-response modeling for the derivation of the RfD. Other issues include the following:

- Presenting the RfD as a single point value or as a range to reflect the inherent imprecision of the RfD;
- Selecting specific guidance documents for derivation of noncancer health effect levels;
- Considering severity of effect in the development of the RfD;
- Using less-than-90-day studies as the basis for RfDs;
- Integrating reproductive/developmental, immunotoxicity, and neurotoxicity data into the RfD calculation;
- Applying toxicokinetic data in risk assessments; and
- Considering the possibility that some noncarcinogenic effects do not exhibit a threshold.

3.2.3.1 Using the Current NOAEL/UF-Based RfD Approach or Adopting More Quantitative Approaches for Noncancer Risk Assessment

The current NOAEL/UF-based RfD methodology, or its predecessor ADI/SF methodology, have been used since 1980. This approach assumes that there is a threshold exposure below which adverse noncancer health effects are not expected to occur. Exposures above this threshold are believed to pose some risk to exposed individuals; however, the current approach does not address the nature and magnitude of the risk above the threshold level (i.e., the shape of the dose-response curve above the threshold). The NOAEL/UF-based RfD approach is intended primarily to ensure that the RfD value derived from the available data falls below the population effects threshold. However, the NOAEL/UF-based RfD procedure has

limitations. In particular, this method requires that one of the actual experimental doses used by the researchers in the critical study be selected as the NOAEL or LOAEL value. The determination that a dose is a NOAEL or LOAEL will depend on the biological endpoints used and the statistical significance of the data. Statistical significance will depend on the number and spacing of dose groups and the numbers of animals used in each dose group. Studies using a small number of animals can limit the ability to distinguish statistically significant differences among measurable responses seen in dose groups and control groups. Furthermore, the determination of the NOAEL or LOAEL also depends on the dose spacing of the study. Doses are often widely spaced, typically differing by factors of three to ten. A study can identify a NOAEL and a LOAEL from among the doses studied, but the "true" effects threshold cannot be determined from those results. The study size and dose spacing limitations also limit the ability to characterize the nature of the expected response to exposures between the observed NOAEL and LOAEL values.

The limitations of the NOAEL/UF approach have prompted development of alternative approaches that incorporate more quantitative dose-response information. The traditional NOAEL approach for noncancer risk assessment has often been a source of controversy and has been criticized in several ways. For example, experiments involving fewer animals tend to produce higher NOAELs and, as a consequence, may produce higher RfDs. Larger sample sizes, on the other hand, should provide greater experimental sensitivity and lower NOAELs. The focus of the NOAEL approach is only on the dose that is the NOAEL, and the NOAEL must be one of the experimental doses. It also ignores the shape of the dose-response curve. Thus, the slope of the dose-response plays little role in determining acceptable exposures for human beings. Therefore, in addition to the NOAEL/UF-based RfD approach described above, EPA will accept other approaches that incorporate more quantitative dose-response information in appropriate situations for the evaluation of noncancer effects and the derivation of RfDs. However, the Agency wishes to emphasize that it still believes the NOAEL/UF RfD methodology is valid and can continue to be used to develop RfDs.

Two alternative approaches that may have relevance in assisting in the derivation of the RfD for a chemical are the BMD and the categorical regression approaches. These alternative approaches may overcome some of the inherent limitations in the NOAEL/UF approach. For example, the BMD analyses for developmental effects show that NOAELs from studies correlate well with a 5 percent response level (Allen et al., 1994). The BMD and the categorical regression approaches usually have greater data requirements than the RfD approach. Thus, it is unlikely that any one approach will apply to every circumstance; in some cases, different approaches may be needed to accommodate the varying databases for the range of chemicals for which water quality criteria must be developed. Acceptable approaches will satisfy the following criteria: (1) meet the appropriate risk assessment goal; (2) adequately describe the toxicity database and its quality; (3) characterize the endpoints properly; (4) provide a measure of the quality of the "fit" of the model when a model is used for dose-response analysis; and (5) describe the key assumptions and uncertainties.

A. The Benchmark Dose

The BMD is defined as the dose estimated to produce a predetermined level of change in response (the Benchmark Response level, or BMR) relative to control. The BMDL is defined as the statistical lower confidence limit on the BMD. In the derivation of an RfD, the BMDL is used as the dose to which uncertainty factors are applied instead of the NOAEL. The BMD approach first models a dose-response curve for the critical effect(s) using available experimental data. Several mathematical algorithms can be used to model the dose-response curve, such as polynomial or Weibull functions. To define a BMD from the modeled curve for quantal data, the assessor first selects the BMR. The choice of the BMR is critical. For quantal endpoints, a particular level of response is chosen (e.g., 1 percent, 5 percent, or 10 percent). For continuous endpoints, the BMR is the degree of change from controls and is based on what is considered a biologically significant change. The BMD is derived from the BMR dose by applying the desired confidence limit calculation. The RfD is obtained by dividing the BMD by one or more uncertainty factors, similar to the NOAEL approach. Because the BMD is used like the NOAEL to obtain the RfD, the BMR should be selected at or near the low end of the range of increased risks that can be detected in a study of typical size. Generally, this falls in the range between the ED_{01} and the ED_{10}.

The Agency will accept use of a BMD approach to derive RfDs for those agents for which there is an adequate database. There are a number of technical decisions associated with the application of the BMD technique. These include the following:

- The definition of an adverse response;
- Selection of response data to model;
- The form of the data used (continuous versus quantal);
- The choice of the measures of increased risk (extra risk versus additional risk);
- The choice of mathematical model (including use of nonstandard models for unusual data sets);
- The selection of the BMR;
- Methods for calculating the confidence interval;
- Selection of the appropriate BMD as the basis for the RfD (when multiple endpoints are modeled from a single study, when multiple models are applied to a single response, and when multiple BMDs are calculated from different studies); and
- The use of uncertainty factors with the BMD approach.

These topics are discussed in detail in Crump et al. (1995) and in the Risk Assessment TSD Volume (USEPA, 2000). The use of the BMD approach has been discussed in general terms by several authors (Gaylor, 1983; Crump, 1984; Dourson et al., 1985; Kimmel and Gaylor, 1988; Brown and Erdreich, 1989; Kimmel, 1990). The International Life Sciences Institute

(ILSI) also held a major workshop on the BMD in September 1993; the workshop proceedings are summarized in ILSI (1993) and in Barnes et al. (1995). For further information on these technical issues, the reader is referred to the publications referenced above.

The BMD approach addresses several of the quantitative or statistical criticisms of the NOAEL approach. These are discussed at greater length in Crump et al. (1995) and are summarized here. First, the BMD approach uses all the dose-response information in the selected study rather than just a single data point, such as the NOAEL or LOAEL. By using response data from all of the dose groups to model a dose-response curve, the BMD approach allows for consideration of the steepness of the slope of the curve when estimating the ED_{10}. The use of the full data set also makes the BMD approach less sensitive to small changes in data than the NOAEL approach, which relies on the statistical comparison of individual dose groups. The BMD approach also allows consistency in the consideration of the level of effect (e.g., a 10 percent response rate) across endpoints.

The BMD approach accounts more appropriately for the size of each dose group than the NOAEL approach. Laboratory tests with fewer animals per dose group tend to yield higher NOAELs, and thus higher RfDs, because statistically significant differences in response rates are harder to detect. Therefore, in the NOAEL approach, dose groups with fewer animals lead to a higher (less conservative) RfD. In contrast, with the BMD approach, smaller dose groups will tend to have the effect of extending the confidence interval around the ED_{10}; therefore, the lower confidence limit on the ED_{10} (the BMD) will be lower. With the BMD approach, greater uncertainty (smaller test groups) leads to a lower (more conservative) RfD.

There are some issues to be resolved before the BMD approach is used routinely. These were identified in a 1996 Peer Consultation Workshop (USEPA, 1996b). Methods for routine use of the BMD are currently under development by EPA. Several RfCs and RfDs based on the BMD approach are included in EPA's IRIS database. These include reference values for methylmercury based on delayed postnatal development in humans; carbon disulfide based on neurotoxicity; 1,1,1,2-tetrafluoroethane based on testicular effects in rats; and antimony trioxide based on chronic pulmonary interstitial inflammation in female rats.

Various mathematical approaches have been proposed for modeling developmental toxicity data (e.g., Crump, 1984; Kimmel and Gaylor, 1988; Rai and Van Ryzin, 1985; Faustman et al., 1989), which could be used to calculate a BMD. Similar methods can be used to model other types of toxicity data, such as neurotoxicity data (Gaylor and Slikker, 1990, 1992; Glowa and MacPhail, 1995). The choice of the mathematical model may not be critical, as long as estimation is within the observed dose range. Since the model fits a mathematical equation to the observed data, the assumptions in a particular model regarding the existence or absence of a threshold for the effect may not be pertinent (USEPA, 1997). Thus, any model that suitably fits the empirical data is likely to provide a reasonable estimate of a BMD. However, research has shown that flexible models that are nonsymmetric (e.g., the Weibull) are superior to symmetric models (e.g., the probit) in estimating the BMD because the data points at the higher doses have less influence on the shape of the curve than at low doses. In addition, models should incorporate fundamental biological factors where such factors are known (e.g., intralitter correlation for developmental toxicity data) in order to account for as much variability in the

data as possible. The Agency is currently using the BMD approach in risk assessments where the data support its use. Draft guidelines for application of the BMD approach also are being developed by the Agency.

Use of BMD methods involves fitting mathematical models to dose-response data obtained primarily from toxicology studies. When considering available models to use for a BMD analysis, it is important to select the model that fits the data the best and is the most biologically appropriate. EPA has developed software following several years of research and development, expert peer review, public comment, subsequent revision, and quality assurance testing. The software (BMDS, Version 1.2) can be downloaded from http://www.epa.gov/ncea/bmds.htm. BMDS facilitates these operations by providing simple data-management tools, a comprehensive help manual, an online help system, and an easy-to-use interface to run multiple models on the same dose-response data.

As part of this software package, EPA has included sixteen (16) different models that are appropriate for the analysis of dichotomous (quantal) data (Gamma, Logistic, Log-Logistic, Multistage, Probit, Log-Probit, Quantal-Linear, Quantal-Quadratic, Weibull), continuous data (Linear, Polynomial, Power, Hill), and nested developmental toxicology data (NLogistic, NCTR, Rai & Van Ryzin). Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and the estimate of the lower-bound confidence limit on the benchmark dose (BMDL). Model results are presented in textual and graphical output files which can be printed or saved and incorporated into other documents.

B. Categorical Regression

Categorical regression is an emerging technique that may have relevance for the derivation of RfDs or for estimating risk above the RfD (Dourson et al., 1997; Guth et al., 1997). The categorical regression approach, like the BMD approach, can be used to estimate a dose that corresponds to a given probability of adverse effects. This dose would then be divided by UFs to establish an RfD. However, unlike the BMD approach, the Categorical regression approach can incorporate information on different health endpoints in a single dose-response analysis. For those health effects for which studies exist, responses to the substance in question are grouped into severity categories; for example (1) no effect, (2) no adverse effect, (3) mild-to-moderate adverse effect, and (4) frank effect. These categories correspond to the dose categories currently used in setting the RfD, namely, the no-observed-effect level (NOEL), NOAEL, LOAEL, and frank-effect level (FEL), respectively. Logistic transformation or other applicable mathematical operations are used to model the probability of experiencing effects in a certain category as a function of dose (Harrell, 1986; Hertzberg, 1989). The “acceptability” of the fit of the model to the data can be judged using several statistical measures, including the χ^2 statistic, correlation coefficients, and the statistical significance of its model parameter estimates.

The resulting mathematical equation can be used to find a dose (or the lower confidence bound on the dose) at which the probability of experiencing adverse effects does not exceed a selected level, e.g., 10 percent. This dose (like the NOAEL or BMD) would then be divided by

relevant UFs to calculate an RfD. For more detail on how to employ the categorical regression approach, see the discussion in the Risk Assessment TSD (USEPA, 2000).

As with the BMD approach, the categorical regression approach has the advantage of using more of the available dose-response data to account for response variability as well as accounting for uncertainty due to sample size through the use of confidence intervals. Additional advantages of categorical regression include the combining of data sets prior to modeling, thus allowing the calculation of the slope of a dose-response curve for multiple adverse effects rather than only one effect at a time. Another advantage is the ability to estimate risks for different levels of severity from exposures above the RfD.

On the other hand, as with BMD, opinions differ over the amount and adequacy of data necessary to implement the method. The categorical regression approach also requires judgments regarding combining data sets, judging goodness-of-fit, and assigning severity to a particular effect. Furthermore, this approach is still in the developmental stage. It is not recommended for routine use, but may be used when data are available and justify the extensive analyses required.

C. Summary

Whether a NOAEL/UF-based methodology, a BMD, a categorical regression model, or other approach is used to develop the RfD, the dose-response-evaluation step of a risk assessment process should include additional discussion about the nature of the toxicity data and its applicability to human exposure and toxicity. The discussion should present the range of doses that are effective in producing toxicity for a given agent; the route, timing, and duration of exposure; species specificity of effects; and any toxicokinetic or other considerations relevant to extrapolation from the toxicity data to human-health-based AWQC. This information should always accompany the characterization of the adequacy of the data.

3.2.3.2 Presenting the RfD as a Single Point or as a Range for Deriving AWQC

Although the RfD has traditionally been presented and used as a single point, its definition contains the phrase ". . . an estimate (with uncertainty spanning perhaps an order of magnitude) . . ." (USEPA, 1993a). Underlying this concept is the reasoning that the selection of the critical effect and the total uncertainty factor used in the derivation of the RfD is based on the "best" scientific judgment, and that competent scientists examining the same database could derive RfDs which varied within an order of magnitude.

In one instance, IRIS presented the RfD as a point value within an accompanying range. EPA derived a single number as the RfD for arsenic (0.3 μg/kg-day), but added that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 μg/kg/day" (USEPA, 1993c). EPA noted that regulatory managers should be aware of the flexibility afforded them through this action.

There are situations in which the risk manager can select an alternative value to use in place of the RfD in the AWQC calculations. The domain from which this alternative value can

be selected is restricted to a defined range around the point estimate. As explained further below, the Agency is recommending that sometimes the use of a value other than the calculated RfD point estimate is appropriate in characterizing risk. The selection of an alternative value within an appropriate range must be determined for each individual situation, since several factors affect the selection of the alternative value. Observing similar effects in several animal species, including humans, can increase confidence in the selection of the critical effect and thereby narrow the range of uncertainty. There are other factors that can affect the precision. These include the slope of the dose-response curve, seriousness of the observed effect, dose spacing, and possibly the route for the experimental doses. Dose spacing and the number of animals in the study groups used in the experiment can also affect the confidence in the RfD.

To derive the AWQC, the calculated point estimate of the RfD is the default. Based on consideration of the available data, the use of another number within the range defined by the product of the UF(s) (and MF, if used) could be justified in some specific situations. This means that there are risk considerations which indicate that some value in the range other than the point estimate may be more appropriate, based on human health or environmental fate considerations. For example, the bioavailability of the contaminant in fish tissues is one factor to consider. If bioavailability from fish tissues is much lower than that from water and the RfD was derived from a study in which the contaminant exposure was from drinking water, the alternative to the calculated RfD could be selected from the high end of the range and justified using the quantitative difference in bioavailability.

Most inorganic contaminants, particularly divalent cations, have bioavailability values of 20 percent or less from a food matrix, but are much more available (about 80 percent or higher) from drinking water. Accordingly, the external dose necessary to produce a toxic internal dose would likely be higher for a study where the exposure occurred through the diet rather than the drinking water. As a result, the RfD from a dietary study would likely be higher than that for the drinking water study if equivalent external doses had been used. Conversely, in cases where the NOAEL that was the basis for the RfD came from a dietary study, the alternative value could be slightly lower than the calculated RfD.

Because the uncertainty around the dose-response relationship increases as extrapolation below the observed data increases, the use of an alternative point within the range may be more appropriate in characterizing the risk than the use of the calculated RfD, especially in situations when the uncertainty is high. Therefore, as a matter of policy, the 2000 Human Health Methodology permits the selection of a single point within a range about the calculated RfD to be used as the basis of the AWQC if an adequate justification of the alternative point is provided. More complete discussion of this option, including limitations on the span of the range, is provided in the Risk Assessment TSD (USEPA, 2000).

3.2.3.3 Guidelines to be Adopted for Derivation of Noncancer Health Effects Values

The Agency currently is using the IRIS background document as the general basis for the risk assessment of noncarcinogenic effects of chemicals (USEPA, 1993a). EPA recommends continued use of this document for this purpose. However, it should be noted that the process for evaluating chemicals for inclusion in IRIS is undergoing revision (USEPA, 1996c). The

revised assessments for many chemicals are now available on IRIS and can be consulted as examples of the RfD development process and required supporting documentation.

3.2.3.4 Treatment of Uncertainty Factors/Severity of Effects During the RfD Derivation and Verification Process

During the RfD derivation and toxicology review process, EPA considers the uncertainty in extrapolating between animal species and within individuals of a species, as well as specific uncertainties associated with the completeness of the database. The Agency's RfD Work Group has always considered the severity of the observed effects induced by the chemical under review when choosing the value of the UF with a LOAEL. For example, during the derivation and verification of the RfD for zinc (USEPA, 1992), an uncertainty factor less than the standard factor of 10 (UF of 3) was assigned to the relatively mild decrease in erythrocyte superoxide dismutase activity in human subjects. EPA recommends that the severity of the critical effect be assessed when deriving an RfD and that risk managers be made aware of the severity of the effect and the weight placed on this attribute of the effect when the RfD was derived.

3.2.3.5 Use of Less-Than-90-Day Studies to Derive RfDs

Generally, less-than-90-day experimental studies are not used to derive an RfD. This is based on the rationale that studies lasting for less than 90 days may be too short to detect various toxic effects. However, EPA, has in certain circumstances, derived an RfD based on a less-than-90-day study. For example, the RfD for nonradioactive effects of uranium is based on a 30-day rabbit study (USEPA, 1989). The short-term exposure period was used, because it was adequate for determining doses that cause chronic toxicity. In other cases, it may be appropriate to use a less-than-90-day study because the critical effect is expressed in less than 90 days. For example, the RfD for nitrate was derived and verified using studies that were less than 3-months in duration (USEPA, 1991b). For nitrate, the critical effect of methemoglobinemia in infants occurs in less than 90 days. When it can be demonstrated from other data in the toxicological database that the critical adverse effect is expressed within the study period and that a longer exposure duration would not exacerbate the observed effect or cause the appearance of some other adverse effect, the Agency may choose to use less-than-90-day studies as the basis of the RfD. Such values would have to be used with care because of the uncertainty in determining if other effects might be expressed if exposure was of greater duration than 90 days.

3.2.3.6 Use of Reproductive/Developmental, Immunotoxicity, and Neurotoxicity Data as the Basis for Deriving RfDs

All relevant toxicity data have some bearing on the RfD derivation and verification and are considered by EPA. The "critical" effect is the adverse effect most relevant to humans or, in the absence of an effect known to be relevant to humans, the adverse effect that occurs at the lowest dose in animal studies. If the critical effect is neurotoxicity, EPA will use that endpoint as the basis for the derivation and verification of an RfD, as it did for the RfD for acrylamide. Moreover, the Agency is continually revising its procedures for noncancer risk assessment. For example, EPA has released guidelines for deriving developmental RfDs (RfD_{DT}, USEPA, 1991a), for using reproductive toxicity (USEPA, 1996a), and neurotoxicity (USEPA, 1995) data

in risk assessments. The Agency is currently working on guidelines for using immunotoxicity data to derive RfDs. In addition, the Agency is proceeding with the process of generating acceptable emergency health levels for hazardous substances in acute exposure situations based on established guidelines (NRC, 1993).

3.2.3.7 Applicability of Toxicokinetic Data in Risk Assessment

All pertinent toxicity data should be used in the risk assessment process, including toxicokinetic and mechanistic data. The Agency has used toxicokinetic data in deriving the RfD for cadmium and other compounds and currently is using toxicokinetic data to better characterize human inhalation exposures from animal inhalation experiments during derivation/verification of RfCs. In analogy to the RfD, the RfC is considered to be an estimate of a concentration in the air that is not anticipated to cause adverse noncancer effects over a lifetime of inhalation exposure (USEPA, 1994; Jarabek, 1995a). For RfCs, different dosimetry adjustments are made to account for the differences between laboratory animals and humans in gas uptake and disposition or in particle clearance and retention. This procedure results in calculation of a "human equivalent concentration." Based on the use of these procedures, an interspecies UF of 3 (i.e., approximately $10^{0.5}$), instead of the standard factor of 10, is used in the RfC derivation (Jarabek, 1995b).

Toxicokinetics and toxicodynamics of a chemical each contribute to a chemical's observed toxicity, and specifically, to observed differences among species in sensitivity. Toxicokinetics describes the disposition (i.e., deposition, absorption, distribution, metabolism, and elimination of chemicals in the body) and can be approximated using toxicokinetic models. Toxicodynamics describes the toxic interaction of the agent with the target cell. In the absence of specific data on their relative contributions to the toxic effects observed in species, each is considered to account for approximately one-half of the difference in observed effects for humans compared with laboratory animals. The implication of this assumption is that an interspecies uncertainty factor of 3 rather than 10 could be used for deriving an RfD when valid toxicokinetic data and models can be applied to obtain an oral "human equivalent applied dose" (Jarabek, 1995b). If specific data exist on the relative contribution of either element to observed effects, that proportion will be used. The role exposure duration may play, and whether or not the chemical or its damage may accumulate over time in a particular scenario, also requires careful consideration (Jarabek, 1995c).

3.2.3.8 Consideration of Linearity (or Lack of a Threshold) for Noncarcinogenic Chemicals

It is quite possible that there are chemicals with noncarcinogenic endpoints that have no threshold for effects. For example, in the case of lead, it has not been possible to identify a threshold for effects on neurological development. Other examples could include genotoxic teratogens and germline mutagens. Genotoxic teratogens act by causing mutational events during organogenesis, histogenesis, or other stages of development. Germline mutagens interact with germ cells to produce mutations which may be transmitted to the zygote and expressed during one or more stages of development. However, there are few chemicals which currently have sufficient mechanistic information about these possible modes of action. It should be recognized that although an MOA consistent with linearity is possible (especially for agents

known to be mutagenic), this has yet to be reasonably demonstrated for most toxic endpoints other than cancer.

EPA has recognized the potential for nonthreshold noncarcinogenic endpoints and discussed this issue in the *Guidelines for Developmental Toxicity Risk Assessment* (USEPA, 1991a) and in the 1986 *Guidelines for Mutagenicity Risk Assessment* (USEPA, 1986). An awareness of the potential for such teratogenic/mutagenic effects should be established in order to deal with such data. However, without adequate data to support a genetic or mutational basis for developmental or reproductive effects, the default becomes a UF or MOA approach, which are procedures utilized for noncarcinogens assumed to have a threshold. Therefore, genotoxic teratogens and germline mutagens should be considered an exception while the traditional uncertainty factor approach is the general rule for calculating criteria or values for chemicals demonstrating developmental/reproductive effects. For the exceptional cases, since there is no well-established mechanism for calculating criteria protective of human health from the effects of these agents, criteria will be established on a case-by-case basis. Other types of nonthreshold noncarcinogens must also be handled on a case-by-case basis.

3.2.3.9 Minimum Data Guidance

For details on minimum data guidance for RfD development, see the Risk Assessment TSD (USEPA, 2000).

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4. EXPOSURE

The derivation of AWQC for the protection of human health requires information about both the toxicological endpoints of concern for water pollutants and the pathways of human exposure to those pollutants. The two primary pathways of human exposure to pollutants present in a particular ambient waterbody that have been considered in deriving AWQC are direct ingestion of drinking water obtained from that waterbody and the consumption of fish/shellfish obtained from that waterbody. The water pathway also includes other exposures from household uses (e.g., showering). The derivation of an AWQC involves the calculation of the maximum water concentration for a pollutant (i.e., the water quality criteria level) that ensures drinking water and/or fish ingestion exposures will not result in human intake of that pollutant in amounts that exceed a specified level based upon the toxicological endpoint of concern.

The equation for noncancer effects is presented again here, in simplified form, to emphasize the exposure-related parameters (in bold). [Note: the RSC parameter also applies to nonlinear low-dose extrapolation for cancer effects and the other exposure parameters apply to all three of the equations (see Section 1.6).]

$$AWQC = RfD \bullet \boldsymbol{RSC} \bullet \frac{(\boldsymbol{BW})}{\left[\boldsymbol{DI} + (\boldsymbol{FI} \bullet BAF)\right]} \qquad \text{(Equation 4-1)}$$

where:

AWQC	=	Ambient Water Quality Criterion (mg/L)
RfD	=	Reference dose for noncancer effects (mg/kg-day)
RSC	=	Relative source contribution factor to account for non-water sources of exposure
BW	=	Human body weight (kg)
DI	=	Drinking water intake (L/day)
FI	=	Fish intake (kg/day)
BAF	=	Bioaccumulation factor (L/kg)

The following subsections discuss exposure issues relevant to the 2000 Human Health Methodology: exposure policy issues; consideration of non-water sources of exposure (the Relative Source Contribution approach); and the factors used in AWQC computation. In relevant sections, science policy and risk management decisions made by EPA are discussed.

4.1 EXPOSURE POLICY ISSUES

This section discusses broad policy issues related to exposure concerning the major objectives that the Agency believes should be met in setting AWQC.

An Exposure Assessment TSD provides greater detail on numerous topics discussed in this guidance: suggested sources of contaminant concentration and exposure intake information; suggestions of survey methods for obtaining and analyzing exposure data necessary for deriving AWQC; summaries of studies on fish consumption among sport fishers and subsistence fishers; more detailed presentation of parameter values (e.g., fish consumption rates, body weights); and additional guidance on the application of the RSC approach.

4.1.1 Sources of Exposure Associated With Ambient Water

4.1.1.1 Appropriateness of Including the Drinking Water Pathway in AWQC

EPA intends to continue including the drinking water exposure pathway in the derivation of its national default human health criteria (AWQC), as has been done since the 1980 AWQC National Guidelines were first published.

EPA recommends inclusion of the drinking water exposure pathway where drinking water is a designated use for the following reasons: (1) Drinking water is a designated use for surface waters under the CWA and, therefore, criteria are needed to assure that this designated use can be protected and maintained. (2) Although rare, there are some public water supplies that provide drinking water from surface water sources without treatment. (3) Even among the majority of water supplies that do treat surface waters, existing treatments may not necessarily be effective for reducing levels of particular contaminants. (4) In consideration of the Agency's goals of pollution prevention, ambient waters should not be contaminated to a level where the burden of achieving health objectives is shifted away from those responsible for pollutant discharges and placed on downstream users to bear the costs of upgraded or supplemental water treatment.

This policy decision has been supported by the States, most of the public stakeholders, and by external peer reviewers. As with the other exposure parameters, States and authorized Tribes have the flexibility to use alternative intake rates if they believe that drinking water consumption is substantively different than EPA's recommended default assumptions of 2 L/day for adults and 1 L/day for children. EPA recommends that States and authorized Tribes use an intake rate that would be protective of a majority of consumers and will consider whether an alternative assumption is adequately protective of a State's or Tribe's population based on the information or rationale provided at the time EPA reviews State and Tribal water quality standards submissions.

4.1.1.2 Setting Separate AWQC for Drinking Water and Fish Consumption

In conjunction with the issue of the appropriateness of including the drinking water pathway explicitly in the derivation of AWQC for the protection of human health, EPA intends to continue its practice of setting a single AWQC for both drinking water and fish/shellfish consumption, and a separate AWQC based on ingestion of fish/shellfish alone. This latter criterion applies in those cases where the designated uses of a waterbody include supporting fishable uses under Section 101(a) of the CWA and, thus, fish or shellfish for human consumption, but not as a drinking water supply source (e.g., non-potable estuarine waters).

EPA does not believe that national water quality criteria for protection of drinking water uses only are particularly useful for two reasons. First, State and Tribal standards for human health are set to protect Section 101(a) uses (e.g., "fishable, swimmable uses") under the CWA. Second, most waters have multiple designated uses. Additionally, the water quality standards program protects aquatic life. The 2000 Human Health Methodology revisions do not change EPA's policy to apply aquatic life criteria to protect aquatic species where they are more sensitive (i.e., when human health criteria would not be protective enough) or where human health via fish or water ingestion is not an issue.

4.1.1.3 Incidental Ingestion from Ambient Surface Waters

The 2000 Human Health Methodology does not routinely include criteria to address incidental ingestion of water from recreational uses. EPA has considered whether there are cases where water quality criteria for the protection of human health based only on fish ingestion (or only criteria for the protection of aquatic life) may not adequately protect recreational users from health effects resulting from incidental water ingestion.

EPA reviewed information that provided estimates of incidental water ingestion rates averaged over time. EPA generally believes that the averaged amount is negligible and will not have any impact on the chemical criteria values representative of both drinking water and fish ingestion. A lack of impact on the criteria values would likely also be true for chemical criteria based on fish consumption only, unless the chemical exhibits no bioaccumulation potential. However, EPA also believes that incidental/accidental water ingestion could be important for the development of microbial contaminant water quality criteria, and for either chemical or microbial criteria for States where recreational uses such as swimming and boating are substantially higher than the national average. EPA also notes that some States have indicated they already have established incidental ingestion rates for use in developing criteria. Therefore, although EPA will not use this intake parameter when deriving its national 304(a) chemical criteria, limited guidance is provided in the Exposure Assessment TSD volume in order to assist States and authorized Tribes that face situations where this intake parameter could be of significance.

4.2 CONSIDERATION OF NON-WATER SOURCES OF EXPOSURE WHEN SETTING AWQC

4.2.1 Policy Background

The 2000 Human Health Methodology uses different approaches for addressing non-water exposure pathways in setting AWQC for the protection of human health depending upon the toxicological endpoint of concern. With those substances for which the appropriate toxic endpoint is carcinogenicity based on a linear low-dose extrapolation, only the two water sources (i.e., drinking water and fish ingestion) are considered in the derivation of the AWQC. Non-water sources are not considered explicitly. In the case of carcinogens based on linear low-dose extrapolation, the AWQC is being determined with respect to the *incremental* lifetime risk posed by a substance's presence in water, and is not being set with regard to an individual's total risk from all sources of exposure. Thus, the AWQC represents the water concentration that would be

expected to increase an individual's lifetime risk of carcinogenicity from exposure to the particular pollutant by no more than one chance in one million, regardless of the additional lifetime cancer risk due to exposure, if any, to that particular substance from other sources.

Furthermore, health-based criteria values for one medium based on linear low-dose extrapolation typically vary from values for other media in terms of the concentration value, and often the associated risk level. Therefore, the RSC concept could not even theoretically apply unless all risk assessments for a particular carcinogen based on linear low-dose extrapolation resulted in the same concentration value and same risk level; that is, an apportionment would need to be based on a single risk value and level.

In the case of substances for which the AWQC is set on the basis of a carcinogen based on a nonlinear low-dose extrapolation or for a noncancer endpoint where a threshold is assumed to exist, non-water exposures are considered when deriving the AWQC using the RSC approach. The rationale for this approach is that for pollutants exhibiting threshold effects, the objective of the AWQC is to ensure that an individual's total exposure does not exceed that threshold level.

There has been some discussion of whether it is, in fact, necessary in most cases to explicitly account for other sources of exposure when computing the AWQC for pollutants exhibiting threshold effects. It has been argued that because of the conservative assumptions generally incorporated in the calculation of RfDs (or POD/UF values) used as the basis for the AWQC derivation, total exposures slightly exceeding the RfD are unlikely to produce adverse effects.

EPA emphasizes that the purpose of the RSC is to ensure that the level of a chemical allowed by a criterion or multiple criteria, when combined with other identified sources of exposure common to the population of concern, will not result in exposures that exceed the RfD or the POD/UF. The policy of considering multiple sources of exposure when deriving health-based criteria has become common in EPA's program office risk characterizations and criteria and standard-setting actions. Numerous EPA workgroups have evaluated the appropriateness of factoring in such exposures, and the Agency concludes that it is important for adequately protecting human health. Consequently, EPA risk management policy has evolved significantly over the last six years. Various EPA program initiatives and policy documents regarding aggregate exposure and cumulative risk have been developed, including the consideration of inhalation and dermal exposures. Additionally, accounting for other exposures has been included in recent mandates (e.g., the Food Quality Protection Act) and, thus, is becoming a requirement for the Agency. The Exposure Decision Tree approach has been shared with other EPA offices, and efforts to coordinate policies on aggregate exposure, where appropriate, have begun. EPA intends to continue developing policy guidance on the RSC issue and guidance to address the concern that human health may not be adequately protected if criteria allow for higher levels of exposure that, combined, may exceed the RfD or POD/UF. EPA also intends to refine the 2000 Human Health Methodology in the future to incorporate additional guidance on inhalation and dermal exposures. As stated previously, EPA is required to derive national water quality criteria under Section 304(a) of the CWA and does not intend to derive site-specific criteria. However, States and authorized Tribes have the flexibility to make alternative exposure and RSC estimates based on local data, and EPA strongly encourages this.

Uncertainty factors used in the derivation of the RfD (or POD/UF) to account for intra- and interspecies variability and the incompleteness of the toxicity data set(s)/animal studies are specifically relevant to the chemical's internal toxicological action, irrespective of the sources of exposure that humans may be experiencing. The Agency's policy is to consider and account for other sources of exposure in order to set protective health criteria. EPA believes that multiple route exposures may be particularly important when uncertainty factors associated with the RfD are small. Although EPA is well aware that RfDs are not all equivalent in their derivation, EPA does not believe that uncertainty in the toxicological data should result in less stringent criteria by ignoring exposure sources. However, the RSC policy approach does allow less stringent assumptions when multiple sources of exposure are not anticipated.

The AWQC are designed to be protective criteria, generally applicable to the waters of the United States. While EPA cannot quantitatively predict the actual human health risk associated with combined exposures above the RfD or POD/UF, a combination of health criteria for multiple media exceeding the RfD or POD/UF may not be sufficiently protective. Therefore, EPA's policy is to routinely account for all sources and routes of non-occupational exposure when setting AWQC for noncarcinogens and for carcinogens based on nonlinear low-dose extrapolations. EPA believes that maintaining total exposure below the RfD (or POD/UF) is a reasonable health goal and that there are circumstances where health-based criteria for a chemical should not exceed the RfD (or POD/UF), either alone (if only one criterion is relevant, along with other intake sources considered as background exposures) or in combination. EPA believes its RSC policy ensures this goal.

Also, given the inability to reasonably predict future changes in exposure patterns, the uncertainties in the exposure estimates due to typical data inadequacy, possible unknown sources of exposure, and the potential for some populations to experience greater exposures than indicated by the available data, EPA believes that utilizing the entire RfD (or POD/UF) does not ensure adequate protection.

4.2.2 The Exposure Decision Tree Approach

As indicated in Section 1, EPA has, in the past, used a "subtraction" method to account for multiple sources of exposure to pollutants. In the subtraction method, other sources of exposure (i.e., those other than the drinking water and fish exposures) are subtracted from the RfD (or POD/UF). However, EPA also previously used a "percentage" method for the same purpose. In this approach, the percentage of total exposure typically accounted for by the exposure source for which the criterion is being determined, referred to as the relative source contribution (RSC), is applied to the RfD to determine the maximum amount of the RfD "apportioned" to that source. With both procedures, a "ceiling" level of 80 percent of the RfD and a "floor level" of 20 percent of the RfD are applied.

The subtraction method is considered acceptable when only one criterion is relevant for a particular chemical. The percentage method is recommended in the context of the above goals when multiple media criteria are at issue. The percentage method does not simply depend on the amount of a contaminant in the prospective criterion source only. It is intended to reflect health considerations, the relative portions of other sources, and the likelihood for ever-changing levels

in each of those multiple sources (due to ever-changing sources of emissions and discharges). Rather than simply defaulting in every instance, the Agency attempts to compare multiple source exposures with one another to estimate their relative contribution to the total–given that understanding the degree to which their concentrations vary, or making any distributional analysis, is often not possible. The criteria levels, when multiple criteria are at issue, are based on the actual levels, with an assumption that there may be enough relative variability such that an apportionment (relating that percentage to the RfD) is a reasonable way of accounting for the uncertainty regarding that variability.

The specific RSC approach recommended by EPA, which we will use for the derivation of AWQC for noncarcinogens and carcinogens assessed using nonlinear low-dose extrapolation, is called the Exposure Decision Tree and is described below. To account for exposures from other media when setting an AWQC (i.e., non-drinking water/non-fish ingestion exposures, and inhalation or dermal exposures), the Exposure Decision Tree for determining proposed RfD or POD/UF apportionments represents a method of comprehensively assessing a chemical for water quality criteria development. This method considers the adequacy of available exposure data, levels of exposure, relevant sources/media of exposure, and regulatory agendas (i.e., whether there are multiple health-based criteria or regulatory standards for the same chemical). The Decision Tree addresses most of the disadvantages associated with the exclusive use of either the percentage or subtraction approaches, because they are not arbitrarily chosen prior to determining the following: specific population(s) of concern, whether these populations are relevant to multiple-source exposures for the chemical in question (i.e., whether the population is actually or potentially experiencing exposure from multiple sources), and whether levels of exposure, regulatory agendas, or other circumstances make apportionment of the RfD or POD/UF desirable. Both subtraction and percentage methods are potentially utilized under different circumstances with the Exposure Decision Tree approach, and the Decision Tree is recommended with the idea that there is enough flexibility to use other procedures if information on the contaminant in question suggests it is not appropriate to follow the Decision Tree. EPA recognizes that there may be other valid approaches in addition to the Exposure Decision Tree.

The Exposure Decision Tree approach allows flexibility in the RfD (or POD/UF) apportionment among sources of exposure. When adequate data are available, they are used to make protective exposure estimates for the population(s) of concern. When other sources or routes of exposure are anticipated but data are not adequate, there is an even greater need to make sure that public health protection is achieved. For these circumstances, a series of qualitative alternatives is used (with the less adequate data or default assumptions) that allow for the inadequacies of the data while protecting human health. Specifically, the Decision Tree makes use of chemical information when actual monitoring data are inadequate. It considers information on the chemical/physical properties, uses of the chemical, and environmental fate and transformation, as well as the likelihood of occurrence in various media. Review of such information, when available, and determination of a reasonable exposure characterization for the chemical will result in a water quality criterion that more accurately reflects exposures than automatically using a default value. Although the 20 percent default will still generally be used when information is not adequate, the need for using it should be reduced. There may also be some situations where EPA would consider the use of an 80 percent default (see Section 4.2.3).

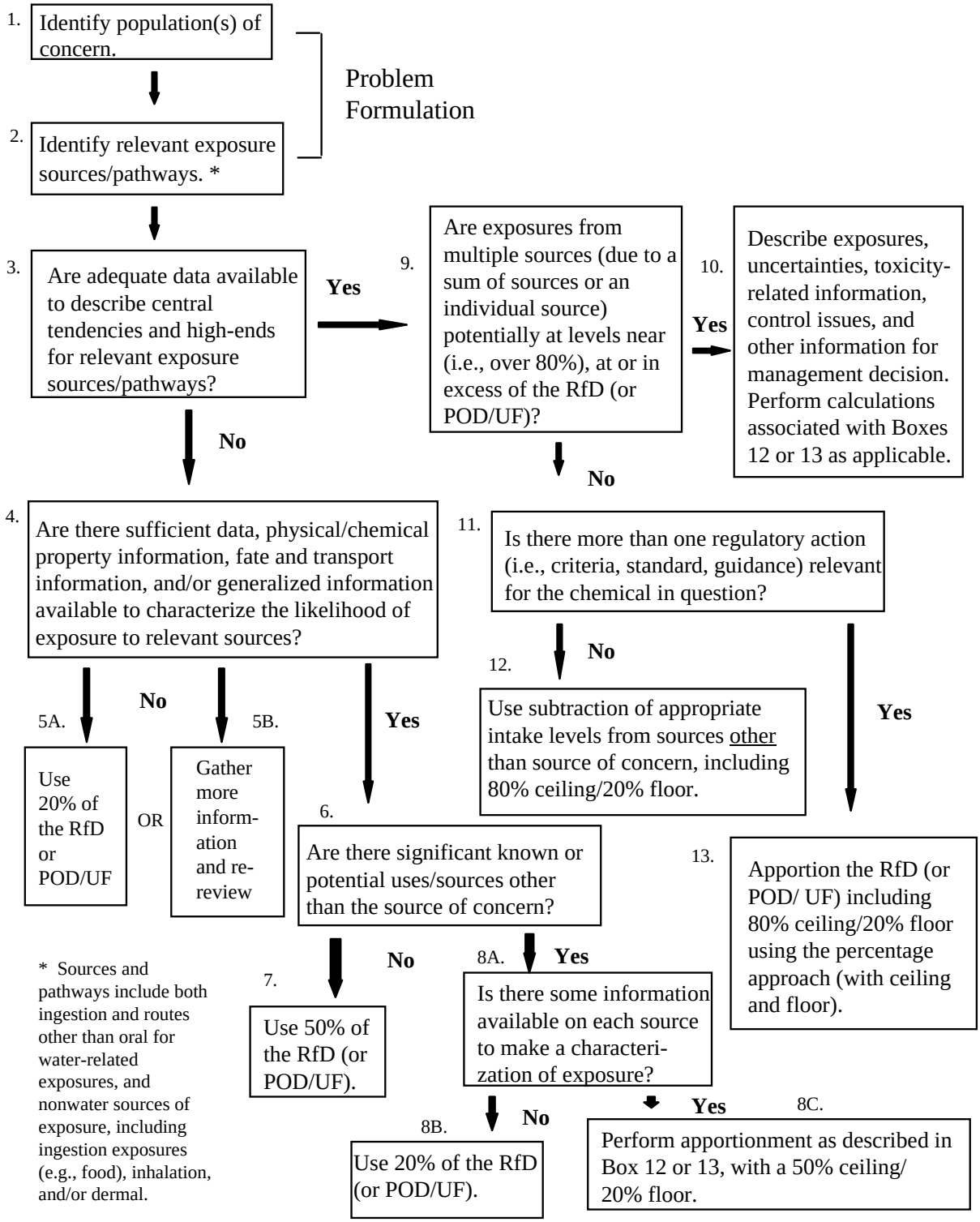
The Decision Tree also allows for use of either the subtraction or percentage method to account for other exposures, depending on whether one or more health-based criterion is relevant for the chemical in question. The subtraction method is considered acceptable when only one criterion is relevant for a particular chemical. In these cases, other sources of exposure can be considered "background" and can be subtracted from the RfD (or POD/UF).

EPA cautions States and Tribes when using the subtraction method in these circumstances. The subtraction method results in a criterion allowing the maximum possible chemical concentration in water after subtracting other sources. As such, it removes any cushion between pre-criteria levels (i.e., actual "current" levels) and the RfD, thereby setting criteria at the highest levels short of exceeding the RfD. It is somewhat counter to the goals of the CWA for maintaining and restoring the nation's waters. It is also directly counter to Agency policies, explicitly stated in numerous programs, regarding pollution prevention. EPA has advocated that it is good health policy to set criteria such that exposures are kept low when current levels are already low. The subtraction method generally results in criteria levels of a contaminant in a particular medium at significantly higher levels than the percentage method and, in this respect, is contradictory to such goals. In fact, many chemicals have pre-criteria levels in environmental media substantially lower (compared to the RfD) than the resulting criteria allow.

When more than one criterion is relevant to a particular chemical, apportioning the RfD (or POD/UF) via the percentage method is considered appropriate to ensure that the combination of criteria and, thus, the potential for resulting exposures do not exceed the RfD (or POD/UF). The Exposure Decision Tree (with numbered boxes) is shown in Figure 4-1. The explanation in the text on the following pages must be read in tandem with the Decision Tree figure; the text in each box of the figure only nominally identifies the process and conditions for determining the outcome for that step of the Decision Tree. The underlying objective is to maintain total exposure below the RfD (or POD/UF) while generally avoiding an extremely low limit in a single medium that represents just a nominal fraction of the total exposure. To meet this objective, all proposed numeric limits lie between 80 percent and 20 percent of the RfD (or POD/UF). Again, EPA will use the Exposure Decision Tree approach when deriving its AWQC but also recognizes that departures from the approach may be appropriate in certain cases. EPA understands that there may be situations where the Decision Tree procedure is not practicable or

Figure 4-1

Exposure Decision Tree for Defining Proposed RfD (or POD/UF) Apportionment



may be simply irrelevant after considering the properties, uses, and sources of the chemical in question. EPA endorses such flexibility by States and authorized Tribes when developing alternative water quality criteria in order to choose other procedures that are more appropriate for setting health-based criteria and, perhaps, apportioning the RfD or POD/UF, as long as reasons are given as to why it is not appropriate to follow the Exposure Decision Tree approach and as long as the steps taken to evaluate the potential sources and levels of exposure are clearly described. Often, however, the common situation of multiple exposure sources for a chemical is likely to merit a Decision Tree evaluation for the purpose of developing human health water quality criteria for a given chemical.

It is clear that this will be an interactive process; input by exposure assessors will be provided to, and received from, risk managers throughout the process, given that there may be significant implications regarding control issues (i.e., cost/feasibility), environmental justice issues, etc. In cases where the Decision Tree is not chosen, communication and concurrence about the decision rationale and the alternative water quality criteria are of great importance.

Descriptions of the boxes within the Decision Tree are separated by the following process headings to facilitate an understanding of the major considerations involved. The decision to perform, or not to perform, an apportionment could actually be made at several points during the Decision Tree process. Working through the process is most helpful for identifying possible exposure sources and the potential for exposure, determining the relevancy of the Decision Tree to developing an AWQC for a particular chemical and, possibly, determining the appropriateness of using an alternative approach to account for overall exposure. "Relevancy" here means determining whether more than one criterion, standard, or other guidance is being planned or is in existence for the chemical in question. Additional guidance for States and Tribes that wish to use the Exposure Decision Tree is provided in the Exposure Assessment TSD.

4.2.2.1 Problem Formulation

Initial Decision Tree discussion centers around the first two boxes: identification of population(s) of concern (Box 1) and identification of relevant exposure sources and pathways (Box 2). The term "problem formulation" refers to evaluating the population(s) and sources of exposure in a manner that allows determination of the potential for the population of concern to experience exposures from multiple sources for the chemical in question. Also, the data for the chemical in question must be representative of each source/medium of exposure and be relevant to the identified population(s). Evaluation includes determining whether the levels, multiple criteria or regulatory standards, or other circumstances make apportionment of the RfD or POD/UF reasonable. The initial problem formulation also determines the exposure parameters chosen, the intake assumptions chosen for each route, and any environmental justice or other social issues that aid in determining the population of concern. The term "data," as used here and discussed throughout this section, refers to ambient sampling data (whether from Federal, regional, State, or area-specific studies) and not internal human exposure measurements.

4.2.2.2 Data Adequacy

In Box 3, it is necessary that adequate data exist for the relevant sources/pathways of exposure if one is to avoid using default procedures. The adequacy of data is a professional judgment for each individual chemical of concern, but EPA recommends that the minimum acceptable data for Box 3 are exposure distributions that can be used to determine, with an acceptable 95 percent confidence interval, the central tendency and high-end exposure levels for each source. In fact, distributional data may exist for some or most of the sources of exposure.

There are numerous factors to consider in order to determine whether a dataset is adequate. These include: (1) sample size (i.e., the number of data points); (2) whether the data set is a random sample representative of the target population (if not, estimates drawn from it may be biased no matter how large the sample); (3) the magnitude of the error that can be tolerated in the estimate (estimator precision); (4) the sample size needed to achieve a given precision for a given parameter (e.g., a larger sample is needed to precisely estimate an upper percentile than a mean or median value); (5) an acceptable analytical method detection limit; and (6) the functional form and variability of the underlying distribution, which determines the estimator precision (e.g., whether the distribution is normal or lognormal and whether the standard deviation is 1 or 10). Lack of information may prevent assessment of each of these factors; monitoring study reports often fail to include background information or sufficient summary statistics (and rarely the raw data) to completely characterize data adequacy. Thus, a case-by-case determination of data adequacy may be necessary.

That being stated, there are some guidelines, as presented below, that lead to a rough rule-of-thumb on what constitutes an "adequate" sample size for exposure assessment. Again, first and foremost, the representativeness of the data for the population evaluated and the analytical quality of the data must be acceptable. If so, the primary objective then becomes estimating an upper percentile (e.g., say the 90th) and a central tendency value of some exposure distribution based on a random sample from the distribution. Assuming that the distribution of exposures is unknown, a nonparametric estimate of the 90th percentile is required. The required estimate, based on a random sample of *n* observations from a target population, is obtained by ranking the data from smallest to largest and selecting the observation whose rank is 1 greater than the largest integer in the product of 0.9 times *n*. For example, in a data set of 25 points, the nonparametric estimate of the 90th percentile is the 23rd largest observation.

In addition to this point estimate, it is useful to have an upper confidence bound on the 90th percentile. To find the rank of the order statistic that gives an upper 95 percent confidence limit on the 90th percentile, the smallest value of *r* that satisfies the following formula is determined:

$$0.95 \approx \sum_{i=0}^{r-1} \binom{n}{i} 0.9^{i}\ 0.1^{n-i} \qquad \text{(Equation 4-2)}$$

where:

r	=	the rank order of the observation
n	=	the number of observations
I	=	integer from 0 to r - 1

For relatively small data sets, the above formula will lead to selecting the largest observation as the upper confidence limit on the 90th percentile. However, the problem with using the maximum is that, in many environmental datasets, the largest observation is an outlier and would provide an unrealistic upper bound on the 90th percentile. It would, therefore, be preferable if the sample size *n* were large enough so that the formula yielded the second largest observation as the confidence limit (see for example Gibbons, 1971).

This motivates establishing the following criterion for setting an "adequate" sample size: pick the smallest *n* such that the nonparametric upper 95 percent confidence limit on the 90th percentile is the second largest value. Application of the above formula with *r* set to *n*-1 yields *n* = 45 for this minimum sample size.

For the upper 95 percent confidence limit to be a useful indicator of a high-end exposure, it must not be overly conservative (too large relative to the 90th percentile). It is, therefore, of interest to estimate the expected magnitude of the ratio of the upper 95 percent confidence limit to the 90th percentile. This quantity generally cannot be computed, since it is a function of the unknown distribution. However, to get a rough idea of its value, consider the particular case of a normal distribution. If the coefficient of variation (i.e., the standard deviation divided by the mean) is between 0.5 and 2.0, the expected value of the ratio in samples of 45 will be approximately 1.17 to 1.31; i.e., the upper 95 percent confidence limit will be only about 17 to 31 percent greater than the 90th percentile on the average.

It should be noted that the nonparametric estimate of the 95 percent upper confidence limit based on the second largest value can be obtained even if the data set has only two detects (it is assumed that the two detects are greater than the detection limit associated with all non-detects). This is an argument for using nonparametric rather than parametric estimation, since use of parametric methods would require more detected values. On the other hand, if non-detects were not a problem and the underlying distribution were known, a parametric estimate of the 90th percentile would generally be more precise.

As stated above, adequacy also depends on whether the samples are relevant to and representative of the population at risk. Data may, therefore, be adequate for some decisions and inadequate for others; this determination requires some professional judgment.

If the answer to Box 3 is no, based on the above determination of adequacy, then the decision tree moves to Box 4. As suggested by the separate boxes, the available data that will be reviewed as part of Box 4 do not meet the requirements necessary for Box 3. In Box 4, any limited data that are available (in addition to information about the chemical/physical properties, uses, and environmental fate and transformation, as well as any other information that would characterize the likelihood of exposure from various media for the chemical) are evaluated to

make a qualitative determination of the relation of one exposure source to another. Although this information should always be reviewed at the outset, it is recommended that this information also be used to estimate the health-based water quality criteria. The estimate should be rather conservative (as indicated in the Decision Tree), given that it is either not based on actual monitoring data or is based on data that has been considered to be inadequate for a more accurate quantitative estimate. Therefore, greater uncertainties exist and accounting for variability is not really possible. Whether the available data are adequate and sufficiently representative will likely vary from chemical to chemical and may depend on the population of concern. If there are some data and/or other information to make a characterization of exposure, a determination can be made as to whether there are significant known or potential uses for the chemical/sources of exposure other than the source of concern (i.e., in this case, the drinking water and fish intakes relevant to developing an AWQC) that would allow one to anticipate/quantify those exposures (Box 6). If there are not, then it is recommended that 50 percent of the RfD or POD/UF can be safely apportioned to the source of concern (Box 7). While this leaves half of the RfD or POD/UF unapportioned, it is recommended as the maximum apportionment due to the lack of data needed to more accurately quantify actual or potential exposures. If the answer to the question in Box 6 is yes (there is multiple source information available for the exposures of concern), and some information is available on each source of exposure (Box 8A), apply the procedure in either Box 12 or Box 13 (depending on whether one or more criterion is relevant to the chemical), using a 50 percent ceiling (Box 8C)–again due to the lack of adequate data. If the answer to the question in Box 8A is no (there is no available information to characterize exposure), then the 20 percent default of the RfD or POD/UF is used (Box 8B).

If the answer to the question in Box 4 is no; that is, there are not sufficient data/information to characterize exposure, EPA intends to generally use the "default" assumption of 20 percent of the RfD or POD/UF (Box 5A) when deriving or revising the AWQC. It may be better to gather more data or information and re-review when this information becomes available (Box 5B). EPA has done this on occasion when resources permit the acquisition of additional data to enable better estimates of exposure instead of the default. If this is not possible, then the assumption of 20 percent of the RfD or POD/UF (Box 5A) should be used. Box 5A is likely to be used infrequently with the Exposure Decision Tree approach, given that the information described in Box 4 should be available in most cases. However, EPA intends to use 20 percent of the RfD (or POD/UF), which has also been used in past water program regulations, as the default value.

4.2.2.3 Regulatory Actions

If there are adequate data available to describe the central tendencies and high ends from each exposure source/pathway, then the levels of exposure relative to the RfD or POD/UF are compared (Box 9). If the levels of exposure for the chemical in question are not near (currently defined as greater than 80 percent), at, or in excess of the RfD or POD/UF, then a subsequent determination is made (Box 11) as to whether there is more than one health-based criterion or regulatory action relevant for the given chemical (i.e., more than one medium-specific criterion,

standard or other guidance being planned, performed or in existence for the chemical). The subtraction method is considered acceptable when only one criterion (standard, etc.) is relevant for a particular chemical. In these cases, other sources of exposure can be considered "background" and can be subtracted from the RfD (or POD/UF). When more than one criterion is relevant to a particular chemical, apportioning the RfD (or POD/UF) via the percentage method is considered appropriate to ensure that the combination of health criteria, and thus the potential for resulting exposures, do not exceed the RfD (or POD/UF).

As indicated in Section 2, for EPA's national 304(a) criteria, the RSC intake estimates of non-water exposures (e.g., non-fish dietary exposures) will be based on arithmetic mean values when data are available. The assumed body weight used in calculating the national criteria will also be based on average values. The drinking water and fish intake values are 90th percentile estimates. EPA believes that these assumptions will be protective of a majority of the population and recommends them for State and Tribal use. However, States and authorized Tribes have the flexibility to choose alternative intake rate and exposure estimate assumptions to protect specific population groups that they have chosen.

4.2.2.4 Apportionment Decisions

If the answer to the question in Box 11 is no (there is not more than one relevant medium-specific criterion/regulatory action), then the recommended method for setting a health-based water quality criterion is to utilize a subtraction calculation (Box 12). Specifically, appropriate intake values for each exposure source other than the source of concern are subtracted out. EPA will rely on average values commonly used in the Agency for food ingestion and inhalation rates, combined with mean contaminant concentration values, for calculating RSC estimates to subtract. Alternatively, contaminant concentrations could be selected based on the variability associated with those concentrations for each source. This implies that a case-by-case determination of the variability and the resulting intake chosen would be made, as each chemical evaluated can be expected to have different variations in concentration associated with each source of intake. However, EPA anticipates that the available data for most contaminants will not allow this for determination (based on past experience). Guidance addressing this possibility is addressed in the Exposure Assessment TSD. EPA does not recommend that high-end intakes be subtracted for every exposure source, since the combination may not be representative of any actually exposed population or individual. The subtraction method would also include an 80 percent ceiling and a 20 percent floor.

If the answer to the question in Box 11 is yes (there is more than one medium-specific criterion/regulation relevant), then the recommended method for setting health-based water quality criteria is to apportion the RfD or POD/UF among those sources for which health-based criteria are being set (Box 13). This is done via a percentage approach (with a ceiling and floor). This simply refers to the percentage of overall exposure contributed by an individual exposure source. For example, if for a particular chemical, drinking water were to represent half of total exposure and diet were to represent the other half, then the drinking water contribution (or RSC) would be 50 percent. The health-based criteria would, in turn, be set at 50 percent of the RfD or POD/UF. This method also utilizes an appropriate combination of intake values for each

exposure source based on values commonly used in the Agency for food ingestion and inhalation rates, combined with mean contaminant concentration values.

Finally, if the levels of exposure for the chemical in question are near (currently defined as greater than 80 percent), at, or in excess of the RfD or POD/UF (i.e., the answer in Box 9 is yes), then the estimates of exposures and related uncertainties, recommended apportionment (either box 12 or 13), toxicity-related information, control issues, and other information are to be presented to managers for a decision (Box 10). The high levels referred to in Box 9 may be due to one source contributing that high level (while other sources contribute relatively little) or due to more than one source contributing levels that, in combination, approach or exceed the RfD or POD/UF. Management input may be necessary due to the control issues (i.e., cost and feasibility concerns), especially when multiple criteria are at issue. In practice, risk managers are routinely a part of decisions regarding regulatory actions and will be involved with any recommended outcome of the Exposure Decision Tree or, for that matter, any alternative to the Exposure Decision Tree. However, because exposures approach or exceed the RfD or POD/UF and because the feasibility of controlling different sources of exposure are complicated issues, risk managers will especially need to be directly involved in final decisions in these circumstances.

It is emphasized here that the procedures in these circumstances are not different than the procedures when exposures are not at or above the RfD (or POD/UF). Therefore, in these cases, estimates should be performed as with Boxes 11, 12, and 13. The recommendation should be made based on health-based considerations only, just as when the chemical in question was not a Box 10 situation. If the chemical is relevant to one health criterion or regulatory action only, the other sources of exposure could be subtracted from the RfD or POD/UF to determine if there is any leftover amount for setting the criterion. If the chemical is a multiple media criteria issue, then an apportionment should be made, even though it is possible that all sources would need to be reduced. Regardless of the outcome of Box 9, all apportionments made (via the methods of Boxes 12 or 13) should include a presentation of the uncertainty in the estimate and in the RfD or POD/UF for a more complete characterization.

The process for a Box 10 situation (versus a situation that is not) differs in that the presentations for Boxes 12 and 13 are based on apportionments (following the review of available information and a determination of appropriate exposure parameters) that must address additional control issues and may result in more selective reductions. With Box 10, one or several criteria possibilities ("scenarios") could be presented for comparison along with implications of the effects of various control options. It is appropriate to present information in this manner to risk managers given the complexity of these additional control issues.

4.2.3 Additional Points of Clarification on the Exposure Decision Tree Approach for Setting AWQC

As with Box 9, if a determination is made in Box 8A (i.e., information is available to characterize exposure) that exposures are near, at, or above the RfD (or POD/UF) based on the available information, the apportionments made need to be presented to risk managers for decision. If information is lacking on some of the multiple exposure sources, then EPA would use a default of 20 percent of the RfD or POD/UF (Box 8B).

Results of both Boxes 12 and 13 rely on the 80 percent ceiling and 20 percent floor. The 80 percent ceiling was implemented to ensure that the health-based goal will be low enough to provide adequate protection for individuals whose total exposure to a contaminant is, due to any of the exposure sources, higher than currently indicated by the available data. This also increases the margin of safety to account for possible unknown sources of exposure. The 20 percent floor has been traditionally rationalized to prevent a situation where small fractional exposures are being controlled. That is, below that point, it is more appropriate to reduce other sources of exposure, rather than promulgating standards for *de minimus* reductions in overall exposure.

If it can be demonstrated that other sources and routes of exposure are not anticipated for the pollutant in question (based on information about its known/anticipated uses and chemical/physical properties), then EPA would use the 80 percent ceiling. EPA qualifies this policy with the understanding that as its policy on cumulative risk assessment continues to develop, the 80 percent RSC may prove to be underprotective.

In the cases of pollutants for which substantial data sets describing exposures across all anticipated pathways of exposure exist, and probabilistic analyses have been conducted based on those data, consideration will be given to the results of those assessments as part of the Exposure Decision Tree approach for setting AWQC.

For many chemicals, the rate of absorption from ingestion can differ substantially from absorption by inhalation. There is also available information for some chemicals that demonstrates appreciable differences in gastrointestinal absorption depending on whether the chemical is ingested from water, soil, or food. For some contaminants, the absorption of the contaminant from food can differ appreciably for plant compared with animal food products. Regardless of the apportionment approach used, EPA recommends using existing data on differences in bioavailability between water, air, soils, and different foods when estimating total exposure for use in apportioning the RfD or POD/UF. The Agency has developed such exposure estimates for cadmium (USEPA, 1994). In the absence of data, EPA will assume equal rates of absorption from different routes and sources of exposure.

4.2.4 Quantification of Exposure

When selecting contaminant concentration values in environmental media and exposure intake values for the RSC analysis, it is important to realize that each value selected (including those recommended as default assumptions in the AWQC equation) may be associated with a distribution of values for that parameter. Determining how various subgroups fall within the distributions of overall exposure and how the combination of exposure variables defines what population is being protected is a complicated and, perhaps, unmanageable task, depending on the amount of information available on each exposure factor included. Many times, the default assumptions used in EPA risk assessments are derived from the evaluation of numerous studies and are considered to generally represent a particular population group or a national average. Therefore, describing with certainty the exact percentile of a particular population that is protected with a resulting criteria is often not possible.

By and large, the AWQC are derived to protect the majority of the general population from chronic adverse health effects. However, as stated above in Section 4.1.1.1, States and authorized Tribes are encouraged to consider protecting population groups that they determine are at greater risk and, thus, would be better protected using alternative exposure assumptions. The ultimate choice of the contaminant concentrations used in the RSC estimate and the exposure intake rates requires the use of professional judgment. This is discussed in greater detail in the Exposure Assessment TSD.

4.2.5 Inclusion of Inhalation and Dermal Exposures

EPA intends to develop policy guidelines to apply to this Methodology for explicitly incorporating inhalation and dermal exposures. When estimating overall exposure to pollutants for AWQC development, EPA believes that the sources of inhalation and dermal exposures considered should include, on a case-by-case basis, both non-oral exposures from water and other inhalation and dermal sources (e.g., ambient or indoor air, soil). When the policy guidelines are completed, this Methodology will be refined to include that guidance.

A number of drinking water contaminants are volatile and thus diffuse from water into the air where they may be inhaled. In addition, drinking water is used for bathing and, thus, there is at least the possibility that some contaminants in water may be dermally absorbed. Volatilization may increase exposure via inhalation and decrease exposure via ingestion and dermal absorption. The net effect of volatilization and dermal absorption upon total exposure to volatile drinking water contaminants is unclear in some cases and varies from chemical to chemical. Dermal exposures are also important to consider for certain population groups, such as children and other groups with high soil contact.

With regard to additional non-water related exposures, it is clear that the type and magnitude of toxicity produced via inhalation, ingestion, and dermal contact may differ; that is, the route of exposure can affect absorption of a chemical and can otherwise modify its toxicity. For example, an inhaled chemical such as hydrogen fluoride may produce localized effects on the lung that are not observed (or only observed at much higher doses) when the chemical is administered orally. Also, the active form of a chemical (and principal toxicity) can be the parent compound and/or one or more metabolites. With this Methodology, EPA recommends that differences in absorption and toxicity by different routes of exposure be determined and accounted for in dose estimates and applied to the exposure assessment. EPA acknowledges that the issue of whether the doses received from inhalation and ingestion exposures are cumulative (i.e., toward the same threshold of toxicity) is complicated. Such a determination involves evaluating the chemical's physical characteristics, speciation, and reactivity. A chemical may also exhibit different metabolism by inhalation versus oral exposure and may not typically be metabolized by all tissues. In addition, a metabolite may be much more or much less toxic than the parent compound. Certainly with a systemic effect, if the chemical absorbed via different routes enters the bloodstream, then there is some likelihood that it will contact the same target organ. Attention also needs to be given to the fact that both the RfD and RfC are derived based on the administered level. Toxicologists generally believe that the effective concentration of the active form of a chemical(s) at the site(s) of action determines the toxicity. If specific differences between routes of exposure are not known, it may be reasonable to assume that the

internal concentration at the site from any route contributes as much to the same effect as any other route. A default of assuming equal absorption has often been used. However, for many of the chemicals that the Agency has reviewed, there is a substantial amount of information already known to determine differences in rates of absorption. For example, absorption is, in part, a function of blood solubility (i.e., Henry's Constant) and better estimations than the default can be made.

The RSC analyses that accompany the 2000 Human Health Methodology accommodate inclusion of inhalation exposures. Even if different target organs are involved between different routes of exposure, a conservative policy may be appropriate to keep all exposures below a certain level. A possible alternative is to set allowable levels (via an equation) such that the total of ingestion exposures over the ingestion RfD added to the total of inhalation exposures over the inhalation RfC is not greater than 1 (Note: the RfD is typically presented in mg/kg-day and the RfC is in mg/m^3). Again, EPA intends to develop guidance for this Methodology to explicitly incorporate inhalation and dermal exposures, and will refine the Methodology when that guidance is completed.

4.3 EXPOSURE FACTORS USED IN THE AWQC COMPUTATION

This section presents values for the specific exposure factors that EPA will use in the derivation of AWQC. These include human body weight, drinking water consumption rates, and fish ingestion rates.

When choosing exposure factor values to include in the derivation of a criterion for a given pollutant, EPA recommends considering values that are relevant to population(s) that is (are) most susceptible to that pollutant. In addition, highly exposed populations should be considered when setting criteria. In general, exposure factor values specific to adults and relevant to lifetime exposures are the most appropriate values to consider when determining criteria to protect against effects from long-term exposure which, by and large, the human health criteria are derived to protect. However, infants and children may have higher rates of water and food consumption per unit body weight compared with adults and also may be more susceptible to some pollutants than adults (USEPA, 1997a). There may be instances where acute or subchronic developmental toxicity makes children the population group of concern. In addition, exposure of pregnant women to certain toxic chemicals may cause developmental effects in the fetus (USEPA, 1997b). Exposures resulting in developmental effects may be of concern for some contaminants and should be considered along with information applicable to long-term health effects when setting AWQC. (See Section 3.2 for further discussion of this issue.) Short-term exposure may include multiple intermittent or continuous exposures occurring over a week or so. Exposure factor values relevant for considering chronic toxicity, as well as exposure factor values relevant for short-term exposure developmental concerns, that could result in adverse health effects are discussed in the sections below. In appropriate situations, EPA may consider developing criteria for developmental health effects based on exposure factor values specific to children or to women of childbearing age. EPA encourages States and Tribes to do the same when health risks are associated with short-term exposures.

EPA believes that the recommended exposure factor default intakes for adults in chronic exposure situations are adequately protective of the population over a lifetime. In providing additional exposure intake values for highly exposed subpopulations (e.g., sport anglers, subsistence fishers), EPA is providing flexibility for States and authorized Tribes to establish criteria specifically targeted to provide additional protection using adjusted values for exposure parameters for body weight, drinking water intake, and fish consumption. The exposure factor values provided for women of childbearing age and children would only be used in the circumstances indicated above.

Each of the following sections recommends exposure parameter values for use in developing AWQC. These are based on both science policy decisions that consider the best available data, as well as risk management judgments regarding the overall protection afforded by the choice in the derivation of AWQC. These will be used by EPA to derive new, or revise existing, 304(a) national criteria.

4.3.1 Human Body Weight Values for Dose Calculations

The source of data for default human body weights used in deriving the AWQC is the third *National Health and Nutrition Examination Survey* (NHANES III). NHANES III represents a very large interview and examination endeavor of the National Center for Health Statistics (NCHS) and included participation from the Centers for Disease Control (CDC). The NHANES III was conducted on a nationwide probability sample of over 30,000 persons from the civilian, non-institutionalized population of the United States. The survey began in October 1988 and was completed in October 1994 (WESTAT, 2000; McDowell, 2000). Body weight data were taken from the NHANES III Examination Data File. Sampling weights were applied to all persons examined in the Mobile Examination Centers (MECs) or at home, as was recommended by the NHANES data analysts (WESTAT, 2000).

The NHANES III survey has numerous strengths and very few weaknesses. Its primary strengths are the national representativeness, large sample size, and precise estimates due to this large sample size. Another strength is its high response rate; the examination rate was 73 percent overall, 89 percent for children under 1 year old, and approximately 85 percent for children 1 to 5 years old (McDowell, 2000). Interview response rates were even higher, but the body weight data come from the NHANES examinations; that is, all body weights were carefully measured by survey staff, rather than the use of self-reported body weights. The only significant potential weakness of the NHANES data is the fact that the data are now between 6 and 12 years old. Given that there were upward trends in body weight from NHANES II to NHANES III, and that NCHS has indicated the prevalence of overweight people increased in all age groups, the data could underestimate current body weights if that trend has continued (WESTAT, 2000).

The NHANES III collected standard body measurements of sample subjects, including height and weight, that were made at various times of the day and in different seasons of the year. This technique was used because one's weight may vary between winter and summer and may fluctuate with recency of food and water intake and other daily activities (McDowell, 2000).

As with the other exposure assumptions, States and authorized Tribes are encouraged to use alternative body weight assumptions for population groups other than the general population and to use local or regional data over default values as more representative of their target population group(s).

4.3.1.1 Rate Protective of Human Health from Chronic Exposure

EPA recommends maintaining the default body weight of 70 kg for calculating AWQC as a representative average value for both male and female adults. As previously indicated, exposure factor values specific to adults are recommended to protect against effects from long-term exposure. The value of 70 kg is based on the following information. In the analysis of the NHANES III database, median and mean values for female adults 18-74 years old are 65.8 and 69.5 kg, respectively (WESTAT, 2000). For males in the same age range, the median and mean values are 79.9 and 82.1 kg, respectively. The mean body weight value for men and women ages 18 to 74 years old from this survey is 75.6 kg (WESTAT, 2000). This mean value is higher than the mean value for adults ages 20-64 years old of 70.5 kg from a study by the National Cancer Institute (NCI) which primarily measured drinking water intake (Ershow and Cantor, 1989). The NCI study is described in the subsection on Drinking Water Intake Rates that follows (Section 4.3.2). The value from the NHANES III database is also higher than the value given in the revised EPA *Exposure Factors Handbook* (USEPA, 1997b), which recommends 71.8 kg for adults, based on the older NHANES II data. The Handbook also acknowledges the commonly used 70 kg value and encourages risk assessors to use values which most accurately reflect the exposed population. However, the point is also made that the 70 kg value is used in the derivation of cancer slope factors and unit risks that appear in IRIS. Consistency is advocated between the dose-response relationship and exposure factors assumed. Therefore, if a value higher than 70 kg is used, the assessor needs to adjust the dose-response relationship as described in the Appendix to Chapter 1, Volume 1 of the Handbook (USEPA, 1997b).

4.3.1.2 Rates Protective of Developmental Human Health Effects

As noted above, pregnant women may represent a more appropriate population for which to assess risks from exposure to chemicals in ambient waters in some cases, because of the potential for developmental effects in fetuses. In these cases, body weights representative of women of childbearing age may be appropriate to adequately protect offspring from such health effects. To determine a mean body weight value appropriate to this population, separate body weight values for women in individual age groups within the range of 15 to 44 years old were analyzed from the NHANES III data (WESTAT, 2000). The resulting median and mean body weight values are 63.2 and 67.3 kg, respectively. Ershow and Cantor (1989) present body weight values specifically for pregnant women included in the survey; median and mean weights are 64.4 and 65.8 kilograms, respectively. Ershow and Cantor (1989), however, do not indicate the ages of these pregnant women. Based on this information for women of childbearing age and pregnant women, EPA recommends use of a body weight value of 67 kg in cases where pregnant women are the specific population of concern and the chemical of concern exhibits reproductive and/or developmental effects (i.e., the critical effect upon which the RfD or POD/UF is based). Using the 67 kg assumption would result in lower (more protective) criteria than criteria based on 70 kg.

As discussed earlier, because infants and children generally have a higher rate of water and food consumption per unit body weight compared with adults, a higher intake rate per unit body weight may be needed when comparing estimated exposure doses with critical doses when RfDs are based on health effects in children. To calculate intake rates relevant to such effects, the body weight of children should be used. As with the default body weight for pregnant women, EPA is not recommending the development of additional AWQC (i.e., similar to drinking water health advisories) that focus on acute or short-term effects, since these are not seen routinely as having a meaningful role in the water quality criteria program. However, there may be circumstances where the consideration of exposures for these groups is warranted. Although the AWQC generally are based on chronic health effects data, they are intended to also be protective with respect to adverse effects that may reasonably be expected to occur as a result of elevated shorter-term exposures. EPA acknowledges this as a potential course of action and is, therefore, recommending these default values which EPA would consider in an appropriate circumstance and for States and authorized Tribes to utilize in such situations.

EPA is recommending an assumption of 30 kg as a default child's body weight to calculate AWQC to provide additional protection for children when the chemical of concern indicates health effects in children are of predominant concern (i.e., test results show children are more susceptible due to less developed immune systems, neurological systems, and/or lower body weights). The value is based on the mean body weight value of 29.9 kg for children ages 1 to14 years old, which combines body weight values for individual age groups within this larger group. The mean value is based on body weight information from NHANES III for individual-year age groups between one and 14 years old (WESTAT, 2000). A mean body weight of 28 kg is obtained using body weight values from Ershow and Cantor (1989) for five age groups within this range of 0-14 years and applying a weighting method for different ages by population percentages from the U.S. Bureau of the Census. The 30 kg assumption is also consistent with the age range for children used with the estimated fish intake rates. Unfortunately, fish intake rates for finer age group divisions are not possible due to the limited sampling base from the fish intake survey; there is limited confidence in calculated values (e.g., the mean) for such fine age groups. Given this limitation, the broad age category of body weight for children is suitable for use with the default fish intake assumption.

Given the hierarchy of preferences regarding the use of fish intake information (see Section 4.3.3), States may have more comprehensive data and prefer to target a more narrow, younger age group. If States choose to specifically evaluate toddlers, EPA recommends using 13 kg as a default body weight assumption for children ages 1 to 3 years old. The median and mean values of body weight for children 1 to 3 years old are 13.2 and 13.1 kg, respectively, based on an analysis of the NHANES III database (WESTAT, 2000). The NHANES III median and mean values for females between 1 and 3 years old are 13.0 and 12.9 kg, respectively, and are 13.4 and 13.4 kg for males, respectively. Median and mean body weight values from the earlier Ershow and Cantor (1989) study for children ages 1 to 3 years old were 13.6 and 14.1 kg, respectively. Finally, if infants are specifically evaluated, EPA recommends a default body weight of 7 kg based on the NHANES III analysis. Median and mean body weights for both male and female infants (combined) 2 months old were 6.3 and 6.3 kg, respectively, and for infants 3 months old were 7.0 and 6.9 kg, respectively. With the broader age category of males and females 2 to 6 months old, median and mean body weights were 7.4 and 7.4 kg, respectively. The NHANES

analysis did not include infants under 2 months of age. Although EPA is not recommending body weight values for newborns, the NCHS National Vital Statistics Report indicates that, for 1997, the median birth weight ranged from 3 to 3.5 kg, according to WESTAT (2000).

Body weight values for individual ages within the larger range of 0-14 years are listed in the Exposure Assessment TSD for those States and authorized Tribes who wish to use body weight values for these individual groups. States and Tribes may wish to consider certain general developmental ages (e.g., infants, pre-adolescents, etc.), or certain specific developmental landmarks (e.g., neurological development in the first four years), depending on the chemical of concern. EPA encourages States and authorized Tribes to choose a body weight intake from the tables presented in the TSD, if they believe a particular age subgroup is more appropriate.

4.3.2 Drinking Water Intake Rates

The basis for the drinking water intake rates (also for the fish intake rates presented in Section 4.3.3) is the 1994-96 Continuing Survey of Food Intake by Individuals *(*CSFII) conducted by the U.S. Department of Agriculture (USDA, 1998). The CSFII survey collects dietary intake information from nationally representative samples of non-institutionalized persons residing in United States households. Households in these national surveys are sampled from the 50 states and the District of Columbia. Each survey collects daily consumption records for approximately 10,000 food codes across nine food groups. These food groups are (1) milk and milk products; (2) meat, poultry, and fish; (3) eggs; (4) dry beans, peas, legumes, nuts, and seeds; (5) grain products; (6) fruit; (7) vegetables; (8) fats, oils, and salad dressings; and (9) sweets, sugars, and beverages. The survey also asks each respondent how many fluid ounces of plain drinking water he or she drank during each of the survey days. In addition, the CSFII collects household information, including the source of plain drinking water, water used to prepare beverages, and water used to prepare foods. Data provide "up-to-date information on food intakes by Americans for use in policy formation, regulation, program planning and evaluation, education, and research." The survey is "the cornerstone of the National Nutritional Monitoring and Related Research Program, a set of related federal activities intended to provide regular information on the nutritional status of the United States population" (USDA, 1998).

The 1994-96 CSFII was conducted according to a stratified, multi-area probability sample organized using estimates of the 1990 United States population. Stratification accounted for geographic location, degree of urbanization, and socioeconomics. Each year of the survey consisted of one sample with oversampling for low-income households.

Survey participants provided two non-consecutive, 24-hour days of dietary data. Both days' dietary recall information was collected by an in-home interviewer. Interviewers provided participants with an instructional booklet and standard measuring cups and spoons to assist them in adequately describing the type and amount of food ingested. If the respondent referred to a cup or bowl in their own home, a 2-cup measuring cup was provided to aid in the calculation of the amount consumed. The sample person could fill their own bowl or cup with water to represent the amount eaten or drunk, and the interviewer could then measure the amount consumed by pouring it into the 2-cup measure. The Day 2 interview occurred three to 10 days

after the Day 1 interview, but not on the same day of the week. The interviews allowed participants "three passes" through the daily intake record to maximize recall (USDA, 1998). Proxy interviews were conducted for children aged six and younger and sampled individuals unable to report due to mental or physical limitations. The average questionnaire administration time for Day 1 intake was 30 minutes, while Day 2 averaged 27 minutes.

Two days of dietary recall data were provided by 15,303 individuals across the three survey years. This constitutes an overall two-day response rate of 75.9 percent. Survey weights were corrected by the USDA for nonresponse.

All three 1994-96 CSFII surveys are multistage, stratified-cluster samples. Sample weights, which project the data from a sampled individual to the population, are based on the probability of an individual being sampled at each stage of the sampling design. The sample weights associated with each individual reporting two days of consumption data were adjusted to correct for nonresponse bias.

The 1994-96 CSFII surveys have advantages and limitations for estimating per capita water (or fish) consumption. The primary advantage of the CSFII surveys is that they were designed and conducted by the USDA to support unbiased estimation of food consumption across the population in the United States and the District of Columbia. Second, the survey is designed to record daily intakes of foods and nutrients and support estimation of food consumption.

One limitation of the 1994-96 CSFII surveys is that individual food consumption data were collected for only two days–a brief period which does not necessarily depict "usual intake." Usual dietary intake is defined as "the long-run average of daily intakes by an individual." Upper percentile estimates may differ for short-term and longer-term data because short-term food consumption data tend to be inherently more variable. It is important to note, however, that variability due to duration of the survey does not result in bias of estimates of overall mean consumption levels. Also, the multistage survey design does not support interval estimates for many of the subpopulations of interest because of sparse representation in the sample. Subpopulations with sparse representation include Native Americans on reservations and certain ethnic groups. While these individuals are participants in the survey, they are not present in sufficient numbers to support consumption estimates.

Despite these limitations, the CSFII is considered one of the best sources of current information on consumption of water and fish-containing foods. The objective of estimating per capita water and fish consumption by the United States population is compatible with the statistical design and scope of the CSFII survey.

4.3.2.1 Rate Protective of Human Health from Chronic Exposure

EPA recommends maintaining the default drinking water intake rate of 2 L/day to protect most consumers from contaminants in drinking water. EPA believes that the 2 L/day assumption is representative of a majority of the population over the course of a lifetime. EPA also notes that there is comparatively little variability in water intake within the population compared with

fish intake (i.e., drinking water intake varies, by and large, by about a three-fold range, whereas fish intake can vary by 100-fold). EPA believes that the 2 L/day assumption continues to represent an appropriate risk management decision. The results of the 1994-96 CSFII analysis indicate that the arithmetic mean, 75th, and 90th percentile values for adults 20 years and older are 1.1, 1.5, and 2.2 L/day, respectively (USEPA, 2000a). The 2 L/day value represents the 86th percentile for adults. These values can also be compared to data from an older National Cancer Institute (NCI) study, which estimated intakes of tapwater in the United States based on the USDA's 1977-78 Nationwide Food Consumption Survey (NFCS). The arithmetic mean, 75th, and 90th percentile values for adults 20 - 64 years old were 1.4, 1.7, and 2.3 L/day, respectively (Ershow and Cantor, 1989). The 2 L/day value represents the 88th percentile for adults from the NCI study.

The 2 L/day assumption was used with the original 1980 AWQC National Guidelines and has also been used in EPA's drinking water program. EPA believes that the newer studies continue to support the use of 2 L/day as a reasonable and protective consumption rate that represents the intake of most water consumers in the general population. However, individuals who work or exercise in hot climates could have water consumption rates significantly above 2 L/day, and EPA believes that States and Tribes should consider regional or occupational variations in water consumption.

4.3.2.2 Rates Protective of Developmental Human Health Effects

Based on the 1994-96 CSFII study data, EPA also recommends 2 L/day for women of childbearing age. The analysis for women of childbearing age (ages 15-44) indicate mean, 75th, and 90th percentile values of 0.9, 1.3, and 2.0 L/day, respectively. These rates compare well with those based on an analysis of tapwater intake by pregnant and lactating women by Ershow et al. (1991), based on the older USDA data, for women ages 15-49. Arithmetic mean, 75th and 90th percentile values were 1.2, 1.5, and 2.2 L/day, respectively, for pregnant women. For lactating women, the arithmetic mean, 75th and 90th percentile values were 1.3, 1.7, and 1.9 L/day, respectively.

As noted above, because infants and children have a higher daily water intake per unit body weight compared with adults, a water consumption rate measured for children is recommended for use when RfDs are based on health effects in children. Use of this water consumption rate should result in adequate protection for infants and children when setting criteria based on health effects for this target population. EPA recommends a drinking water intake of 1 L/day to, again, represent a majority of the population of children that consume drinking water. The results of the 1994-96 CSFII analysis indicate that for children from 1 to 10 years of age, the arithmetic mean, 75th, and 90th percentile values are 0.4, 0.6, and 0.9 L/day, respectively (USEPA, 2000a). The 1 L/day value represents the 93rd percentile for this group. The arithmetic mean, 75th, and 90th percentile values for smaller children, ages 1 to 3 years, are 0.3, 0.5, and 0.7 L/day, respectively. The 1 L/day value represents the 97th percentile of the group ages 1 to 3 years old. For the category of infants under 1 year of age, the arithmetic mean, 75th, and 90th percentile values are 0.3, 0.7, and 0.9 L/day, respectively. These data can similarly be compared to those of the older National Cancer Institute (NCI) study. The arithmetic mean, 75th, and 90th percentile values for children 1 to 10 years old were 0.74, 0.96, and 1.3 L/day,

respectively. The mean, 75th, and 90th percentile values for children 1 to 3 years old in the NCI study were 0.6, 0.8, and 1.2 L/day, respectively. Finally, the mean, 75th, and 90th percentile values for infants less than 6 months old were 0.3, 0.3, and 0.6 L/day, respectively (Ershow and Cantor, 1989).

4.3.2.3 Rates Based on Combining Drinking Water Intake and Body Weight

As an alternative to considering body weight and drinking water intake rates separately, EPA is providing rates based on intake per unit body weight data (in units of ml/kg) in the Exposure Assessment TSD, with additional discussion on their use. These rates are based on self-reported body weights from the CSFII survey respondents for the 1994-96 data. While EPA intends to derive or revise national default criteria on the separate intake values and body weights, in part due to the strong input received from its State stakeholders, the ml/kg-BW/day values are provided in the TSD for States or authorized Tribes that prefer their use. It should be noted that in their 1993 review, EPA's Science Advisory Board (SAB) felt that using drinking water intake rate assumptions on a per unit body weight basis would be more accurate, but did not believe this change would appreciably affect the criteria values (USEPA, 1993).

4.3.3 Fish Intake Rates

The basis for the fish intake rates is the 1994-96 CSFII conducted by the USDA, and described above in Section 4.3.2.

4.3.3.1 Rates Protective of Human Health from Chronic Exposure

EPA recommends a default fish intake rate of 17.5 grams/day to adequately protect the general population of fish consumers, based on the 1994 to 1996 data from the USDA's CSFII Survey. EPA will use this value when deriving or revising its national 304(a) criteria. This value represents the 90th percentile of the 1994-96 CSFII data. This value also represents the uncooked weight estimated from the CSFII data, and represents intake of freshwater and estuarine finfish and shellfish only. For deriving AWQC, EPA has also considered the States' and Tribes' needs to provide adequate protection from adverse health effects to highly exposed populations such as recreational and subsistence fishers, in addition to the general population. Based on available studies that characterize consumers of fish, recreational fishers and subsistence fishers are two distinct groups whose intake rates may be greater than the general population. It is, therefore, EPA's decision to discuss intakes for these two groups, in addition to the general population.

EPA recommends default fish intake rates for recreational and subsistence fishers of 17.5 grams/day and 142.4 grams/day, respectively. These rates are also based on uncooked weights for fresh/estuarine finfish and shellfish only. However, because the level of fish intake in highly exposed populations varies by geographical location, EPA suggests a four preference hierarchy for States and authorized Tribes to follow when deriving consumption rates that encourages use of the best local, State, or regional data available. A thorough discussion of the development of this policy method and relevant data sources is contained in the Exposure Assessment TSD. The hierarchy is also presented here because EPA strongly emphasizes that States and authorized

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Tribes should consider developing criteria to protect highly exposed population groups and use local or regional data over the default values as more representative of their target population group(s). The four preference hierarchy is: (1) use of local data; (2) use of data reflecting similar geography/population groups; (3) use of data from national surveys; and (4) use of EPA's default intake rates.

The recommended four preference hierarchy is intended for use in evaluating fish intake from fresh and estuarine species only. Therefore, to protect humans who additionally consume marine species of fish, the marine portion should be considered an *other source of exposure* when calculating an RSC for dietary intake. Refer to the Exposure Assessment TSD for further discussion. States and Tribes need to ensure that when evaluating overall exposure to a contaminant, marine fish intake is not double-counted with the other dietary intake estimate used. Coastal States and authorized Tribes that believe accounting for total fish consumption (i.e., fresh/estuarine and marine species) is more appropriate for protecting the population of concern may do so, provided that the marine intake component is not double-counted with the RSC estimate. Tables of fish consumption intakes based on the CSFII in the TSD provide rates for fresh/estuarine species, marine species, and total (combined) values to facilitate this option for States and Tribes. Throughout this section, the terms "fish intake" or "fish consumption" are used. These terms refer to the consumption of finfish and shellfish, and the CSFII survey includes both. States and Tribes should ensure that when selecting local or regionally-specific studies, both finfish and shellfish are included when the population exposed are consumers of both types.

EPA's first preference is that States and authorized Tribes use the results from fish intake surveys of local watersheds within the State or Tribal jurisdiction to establish fish intake rates that are representative of the defined populations being addressed for the particular waterbody. Again, EPA recommends that data indicative of fresh/estuarine species only be used which is, by and large, most appropriate for developing AWQC. EPA also recommends the use of uncooked weight intake values, which is discussed in greater detail with the fourth preference. States and authorized Tribes may use either high-end values (such as the 90^{th} or 95^{th} percentile values) or average values for an identified population that they plan to protect (e.g., subsistence fishers, sport fishers, or the general population). EPA generally recommends that arithmetic mean values should be the lowest value considered by States or Tribes when choosing intake rates for use in criteria derivation. When considering geometric mean (median) values from fish consumption studies, States and authorized Tribes need to ensure that the distribution is based on survey respondents who reported consuming fish because surveys based on both consumers and nonconsumers can often result in median values of zero. If a State or Tribe chooses values (whether the central tendency or high-end values) from studies that particularly target high-end consumers, these values should be compared to high-end fish intake rates for the general population to make sure that the high-end consumers within the general population would be protected by the chosen intake rates. EPA believes this is a reasonable procedure and is also consistent with the recent Great Lakes Water Quality Initiative (known as the "GLI") (USEPA, 1995). States and authorized Tribes may wish to conduct their own surveys of fish intake, and EPA guidance is available on methods to conduct such studies in *Guidance for Conducting Fish and Wildlife Consumption Surveys* (USEPA, 1998). Results from broader geographic regions in which the State or Tribe is located can also be used, but may not be as applicable as results from

local watersheds. Since such studies would ultimately form the basis of a State or Tribe's AWQC, EPA would review any surveys of fish intake for consistency with the principles of EPA's guidance as part of the Agency's review of water quality standards under Section 303(c).

If surveys conducted in the geographic area of the State or Tribe are not available, EPA's second preference is that States and authorized Tribes consider results from existing fish intake surveys that reflect similar geography and population groups (e.g., from a neighboring State or Tribe or a similar watershed type), and follow the method described above regarding target values to derive a fish intake rate. Again, EPA recommends the use of uncooked weight intake values and the use of fresh/estuarine species data only. Results of existing local and regional surveys are discussed in greater detail in the TSD.

If applicable consumption rates are not available from local, State, or regional surveys, EPA's third preference is that States and authorized Tribes select intake rate assumptions for different population groups from national food consumption surveys. EPA has analyzed one such national survey, the 1994-96 CSFII. As described in Section 4.3.2, this survey, conducted annually by the USDA, collects food consumption information from a probability sample of the population of all 50 states. Respondents to the survey provide two days of dietary recall data. A detailed description of the combined 1994-96 CSFII survey, the statistical methodology, and the results and uncertainties of the EPA analyses are provided in a separate EPA report (USEPA, 2000b). The Exposure Assessment TSD for this Methodology presents selected results from this report including point and interval estimates of combined finfish and shellfish consumption for the mean, 50^{th} (median), 90^{th}, 95^{th}, and 99^{th} percentiles. The estimated fish consumption rates are by fish habitat (i.e., freshwater/estuarine, marine and all habitats) for the following population groups: (1) all individuals; (2) individuals age 18 and over; (3) women ages 15-44; and (4) children age 14 and under. Three kinds of estimated fish consumption rates are provided: (1) per capita rates (i.e., rates based on consumers and nonconsumers of fish from the survey period– refer to the TSD for further discussion); (2) consumers-only rates (i.e., rates based on respondents who reported consuming finfish or shellfish during the two-day reporting period); and (3) per capita consumption by body weight (i.e., per capita rates reported as milligrams of fish per kilogram of body weight per day).

EPA's fourth preference is that States and authorized Tribes use as fish intake assumptions the following default rates, based on the 1994-96 CSFII data, that EPA believes are representative of fish intake for different population groups: 17.5 grams/day for the general adult population and sport fishers, and 142.4 grams/day for subsistence fishers. These are risk management decisions that EPA has made after evaluating numerous fish intake surveys. These values represent the uncooked weight intake of freshwater/estuarine finfish and shellfish. As with the other preferences, EPA requests that States and authorized Tribes routinely consider whether there is a substantial population of sport fishers or subsistence fishers when developing site-specific estimates, rather than automatically basing them on the typical individual. Because the combined 1994-96 CSFII survey is national in scope, EPA will use the results from this survey to estimate fish intake for deriving national criteria. EPA has recognized the data gaps and uncertainties associated with the analysis of the 1994-96 CSFII survey in the process of making its default recommendations. The estimated mean of freshwater and estuarine fish ingestion for adults is 7.50 grams/day, and the median is 0 grams/day. The estimated 90^{th}

percentile is 17.53 grams/day; the estimated 95th percentile is 49.59 grams/day; and the estimated 99th percentile is 142.41 grams/day. The median value of 0 grams/day may reflect the portion of individuals in the population who never eat fish as well as the limited reporting period (2 days) over which intake was measured. By applying as a default 17.5 grams/day for the general adult population, EPA intends to select an intake rate that is protective of a majority of the population (again, the 90th percentile of consumers and nonconsumers according to the 1994-96 CSFII survey data). Trophic level breakouts are: TL2 = 3.8 grams/day; TL3 = 8.0 grams/day; and TL4 = 5.7 grams/day. EPA further considers 17.5 grams/day to be indicative of the average consumption among sport fishers based on averages in the studies reviewed, which are presented in the Exposure Assessment TSD. Similarly, EPA believes that the assumption of 142.4 grams/day is within the range of average consumption estimates for subsistence fishers based on the studies reviewed. Experts at the 1992 National Workshop that initiated the effort to revise this Methodology acknowledged that the national survey high-end values are representative of average rates for highly exposed groups such as subsistence fishermen, specific ethnic groups, or other highly exposed people. EPA is aware that some local and regional studies indicate greater consumption among Native American, Pacific Asian American, and other subsistence consumers, and recommends the use of those studies in appropriate cases, as indicated by the first and second preferences. Again, States and authorized Tribes have the flexibility to choose intake rates higher than an average value for these population groups. If a State or authorized Tribe has not identified a separate well-defined population of high-end consumers and believes that the national data from the 1994-96 CSFII are representative, they may choose these recommended rates.

As indicated above, the default intake values are based on the uncooked weights of the fish analyzed. There has been some question regarding whether to use cooked or uncooked weights of fish intake for deriving the AWQC. Studies show that, typically, with a filet or steak of fish, the weight loss in cooking is about 20 percent; that is, the uncooked weight is approximately 20 percent higher (Jacobs et al., 1998). This obviously means that using uncooked weights results in a slightly higher intake rate and slightly more stringent AWQC. In researching consumption surveys for this proposal, EPA has found that some surveys have reported rates for cooked fish, others have reported uncooked rates, and many more are unclear as to whether cooked or uncooked rates are used. The basis of the CSFII survey was prepared or *as consumed* intakes; that is, the survey respondents estimated the weight of fish that they consumed. This was also true with the GLI (which was specifically based on studies describing consumption rates of cooked fish) and, by and large, cooked fish is what people consume. However, EPA's *Guidance For Assessing Chemical Contaminant Data For Use In Fish Advisories* recommends analysis and advisories based on uncooked fish (USEPA, 1997a). EPA considered the potential confusion over the fact that the uncooked weights are used in the fish advisory program. Further, the measures of a contaminant in fish tissue samples that are applicable to compliance monitoring and the permitting program are related to the uncooked weights. The choice of intakes is also complicated by factors such as the effect of the cooking process, the different parts of a fish where a chemical may accumulate, and the method of preparation.

After considering all of the above (in addition to public input received), EPA will derive its national default criteria based on the uncooked weight fish intakes. The Exposure

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Assessment TSD provides additional guidance on site-specific modifications. Specifically, an alternate approach is described for calculating AWQC with the *as consumed* weight–which is more directly associated with human exposure and risk–and then adjusting the value by the approximate 20 percent loss to an uncooked equivalent (thereby representing the same relative risk as the *as consumed* value). This approach results in a different AWQC value (than using the uncooked weights) and represents a more direct translation of the *as consumed* risk to the uncooked equivalent. However, EPA understands that it is more scientifically rigorous and may be too intensive of a process for States and Tribes to rely on. The option is presented in the TSD to offer States and authorized Tribes greater flexibility with their water quality standards program.

The default fish intake values also reflect specific designations of species classified in accordance with information regarding the life history of the species or based on landings information form the National Marine Fisheries Service. Most significantly, salmon has been reclassified from a freshwater/estuarine species to a marine species. As marine harvested salmon represents approximately 99 percent of salmon consumption in the 1994-96 CSFII Survey, removal reduces the overall fresh/estuarine fish consumption rate by 13 percent. Although they represent a very small percentage of freshwater/estuarine intake, land-locked and farm-raised salmon consumed by 1994-96 CSFII respondents are still included. The rationale for the default intake species designations is explained in the Exposure Assessment TSD. Once again, EPA emphasizes the flexibility for States and authorized Tribes to use alternative assumptions based on local or regional data to better represent their population groups of concern.

4.3.3.2 Rates Protective of Developmental Human Health Effects

Exposures resulting in health effects in children or developmental effects in fetuses may be of primary concern. As discussed at the beginning of this section on exposure factors used, in a situation where acute or sub-chronic toxicity and exposure are the basis of an RfD (or POD/UF), EPA will consider basing its national default criteria on children or women of childbearing age, depending on the target population at greatest risk. EPA recommends that States and authorized Tribes use exposure factors for children or women of childbearing age in these situations. As stated previously, EPA is not recommending the development of additional AWQC but is acknowledging that basing a criterion on these population groups is a potential course of action and is, therefore, recommending the following default intake rates for such situations.

EPA's preferences for States and authorized Tribes in selecting values for intake rates relevant for children is the same as that discussed above for establishing values for average daily consumption rates for chronic effects; i.e., in decreasing order of preference, results from fish intake surveys of local watersheds, results from existing fish intake surveys that reflect similar geography and population groups, the distribution of intake rates from nationally based surveys (e.g., the CSFII), or lastly, the EPA default rates. When an RfD is based on health effects in children, EPA recommends a default intake rate of 156.3 grams/day for assessing those contaminants that exhibit adverse effects. This represents the 90th percentile consumption rate for actual consumers of freshwater/estuarine finfish and shellfish for children ages 14 and under using the combined 1994 to 1996 results from the CSFII survey. The value was calculated based

on data for only those children who ate fish during the 2-day survey period, and the intake was averaged over the number of days during which fish was actually consumed. EPA believes that by selecting the data for consumers only, the 90th percentile is a reasonable intake rate to approximate consumption of fresh/estuarine finfish and shellfish within a short period of time for use in assessments where adverse effects in children are of primary concern. As discussed previously, EPA will use a default body weight of 30 kg to address potential acute or subchronic effects from fish consumption by children. EPA is also providing these default intake values for States and authorized Tribes that choose to provide additional protection when developing criteria that they believe should be based on health effects in children. This is consistent with the rationale in the recent GLI (USEPA, 1995) and is an approach that EPA believes is reasonable. Distributional information on intake values relevant for assessing exposure when health effects to children are of concern is presented in the Exposure Assessment TSD.

There are also cases in which pregnant women may be the population of most concern, due to the possibility of developmental effects that may result from exposures of the mother to toxicants. In these cases, fish intake rates specific to females of childbearing age are most appropriate when assessing exposures to developmental toxicants. When an RfD is based on developmental toxicity, EPA proposes a default intake rate of 165.5 grams/day for assessing exposures for women of childbearing age from contaminants that cause developmental effects. This is equivalent to the 90th percentile consumption rate for actual consumers of freshwater/ estuarine finfish and shellfish for women ages 15 to 44 using the combined 1994 to1996 results from the CSFII survey. As with the rate for children, this value represents only those women who ate fish during the 2-day survey period. As discussed previously, EPA will use a default body weight of 67 kg for women of childbearing age.

4.3.3.3 Rates Based on Combining Fish Intake and Body Weight

As with the drinking water intake values, EPA is providing values for fish intake based on a per unit body weight basis (in units of mg/kg) in the Exposure Assessment TSD. These rates use the self-reported body weights of the 1994-96 CSFII survey. Again, while EPA intends to derive or revise national default criteria on the separate intake values and body weights, the mg/kg-BW/day values are provided in the TSD for States or authorized Tribes that prefer their use.

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5. BIOACCUMULATION

5.1 INTRODUCTION

Aquatic organisms can accumulate certain chemicals in their bodies when exposed to these chemicals through water, their diet, and other sources. This process is called bioaccumulation. The magnitude of bioaccumulation by aquatic organisms varies widely depending on the chemical but can be extremely high for some highly persistent and hydrophobic chemicals. For such highly bioaccumulative chemicals, concentrations in aquatic organisms may pose unacceptable human health risks from fish and shellfish consumption even when concentrations in water are too low to cause unacceptable health risks from drinking water consumption alone. These chemicals may also biomagnify in aquatic food webs, a process whereby chemical concentrations increase in aquatic organisms of each successive trophic level due to increasing dietary exposures (e.g., increasing concentrations from algae, to zooplankton, to forage fish, to predatory fish).

In order to prevent harmful exposures to waterborne chemicals through the consumption of contaminated fish and shellfish, national 304(a) water quality criteria for the protection of human health must address the process of chemical bioaccumulation in aquatic organisms. For deriving national 304(a) criteria to protect human health, EPA accounts for potential bioaccumulation of chemicals in fish and shellfish through the use of national bioaccumulation factors (BAFs). A national BAF is a ratio (in L/kg) that relates the concentration of a chemical in water to its expected concentration in commonly consumed aquatic organisms in a specified trophic level. An illustration of how national BAFs are used in the derivation of 304(a) criteria for carcinogens using linear low-dose extrapolation is shown in the following equation:

$$AWQC = RSD \bullet \left(\frac{BW}{DI + \sum_{i=2}^{4} (FI_i \bullet BAF_i)} \right) \qquad \text{(Equation 5-1)}$$

where:

RSD	=	Risk specific dose (mg/kg-day)
BW	=	Human body weight (kg)
DI	=	Drinking water intake (L/day)
FI_i	=	Fish intake at trophic level I, where I=2, 3, and 4;
BAF_i	=	National bioaccumulation factor at trophic level I, where I=2, 3, and 4

The purpose of this chapter is to present EPA's recommended methodology for deriving national bioaccumulation factors for setting national 304(a) water quality criteria to protect human health. A detailed scientific basis of the recommended national BAF methodology is provided in the Bioaccumulation TSD. While the methodology detailed in this chapter is

intended to be used by EPA for deriving national BAFs, EPA encourages States and authorized Tribes to derive BAFs that are specific to certain regions or waterbodies, where appropriate. Guidance to States and authorized Tribes for deriving site-specific BAFs is provided in the Biaccumulation TSD.

5.1.1 Important Bioaccumulation and Bioconcentration Concepts

Several attributes of the bioaccumulation process are important to understand when deriving national BAFs for use in setting national 304(a) criteria. First, the term "bioaccumulation" refers to the uptake and retention of a chemical by an aquatic organism from all surrounding media (e.g., water, food, sediment). The term "bioconcentration" refers to the uptake and retention of a chemical by an aquatic organism from water only. For some chemicals (particularly those that are highly persistent and hydrophobic), the magnitude of bioaccumulation by aquatic organisms can be substantially greater than the magnitude of bioconcentration. Thus, an assessment of bioconcentration alone would underestimate the extent of accumulation in aquatic biota for these chemicals. Accordingly, EPA's guidelines presented in this chapter emphasize the measurement of chemical bioaccumulation by aquatic organisms, whereas EPA's 1980 Methodology emphasized the measurement of bioconcentration.

Another noteworthy aspect of bioaccumulation process is the issue of steady-state conditions. Specifically, both bioaccumulation and bioconcentration can be viewed simply as the result of competing rates of chemical uptake and depuration (chemical loss) by an aquatic organism. The rates of chemical uptake and depuration can be affected by various factors including the properties of the chemical, the physiology of the organism in question, water quality and other environmental conditions, ecological characteristics of the waterbody (e.g., food web structure), and the concentration and loadings history of the chemical. When the rates of chemical uptake and depuration are equal, tissue concentrations remain constant over time and the distribution of the chemical between the organism and its source(s) is said to be at steady-state. For constant chemical exposures and other conditions, the steady-state concentration in the organism represents the highest accumulation potential of the chemical in that organism under those conditions. The time required for a chemical to achieve steady state has been shown to vary according to the properties of the chemical and other factors. For example, some highly hydrophobic chemicals can require long periods of time to reach steady state between environmental compartments (e.g., many months), while highly hydrophilic chemicals usually reach steady-state relatively quickly (e.g., hours to days).

Since national 304(a) criteria for the protection of human health are typically designed to protect humans from harmful lifetime or long-term exposures to waterborne contaminants, the assessment of bioaccumulation that equals or approximates steady-state accumulation is one of the principles underlying the derivation of national BAFs. For some chemicals that require relatively long periods of time to reach steady-state in tissues of aquatic organisms, changes in water column concentrations may occur on a much more rapid time scale compared to the corresponding changes in tissue concentrations. Thus, if the system departs substantially from steady-state conditions and water concentrations are not averaged over a sufficient time period, the ratio of the tissue concentration to a water concentration may have little resemblance to the steady-state ratio and have little predictive value of long-term bioaccumulation potential.

Therefore, BAF measurements should be based on water column concentrations which are averaged over a sufficient period of time (e.g., a duration comparable to the time required for the chemical to reach steady-state). In addition, BAF measurements should be based on adequate spatial averaging of both tissue and water column concentrations for use in deriving 304(a) criteria for the protection of human health.

For this reason, a BAF is defined in this Methodology as representing the ratio (in L/kg-tissue) of a concentration of a chemical in tissue to its concentration in the surrounding water in situations where the organism and its food are exposed and the ratio does not change substantially over time (i.e., the ratio which reflects bioaccumulation at or near steady-state). A bioconcentration factor (BCF) is the ratio (in L/kg-tissue) of the concentration of a substance in tissue of an aquatic organism to its concentration in the ambient water, in situations where the organism is exposed through the water only and the ratio does not change substantially over time.

5.1.2 Goal of the National BAF

The goal of EPA's national BAF is to represent the long-term, average bioaccumulation potential of a chemical in edible tissues of aquatic organisms that are commonly consumed by humans throughout the United States. National BAFs are not intended to reflect fluctuations in bioaccumulation over short time periods (e.g., a few days) because 304(a) human health criteria are generally designed to protect humans from long-term exposures to waterborne chemicals. National BAFs are also intended to account for some major chemical, biological, and ecological attributes that can affect bioaccumulation in bodies of water across the United States. For example, separate procedures are provided for deriving national BAFs depending on the type of chemical (i.e., nonionic organic, ionic organic, inorganic and organometallic). In addition, EPA's national BAFs are derived separately for each trophic level to account for potential biomagnification of some chemicals in aquatic food webs and broad physiological differences between trophic levels that may influence bioaccumulation. Because lipid content of aquatic organisms and the amount of organic carbon in the water column have been shown to affect bioaccumulation of nonionic organic chemicals, EPA's national BAFs are adjusted to reflect the lipid content of commonly consumed fish and shellfish and the freely dissolved fraction of the chemical in ambient water for these chemicals.

5.1.3 Changes to the 1980 Methodology

Numerous scientific advances have occurred in the area of bioaccumulation since the publication of the 1980 Methodology for deriving AWQC for the protection of human health (USEPA, 1980). These advances have significantly increased our ability to assess and predict the bioaccumulation of chemicals in aquatic biota. As a result, EPA has revised the bioaccumulation portion of the 1980 Methodology to reflect the current state of the science and to improve accuracy in assessing bioaccumulation for setting 304(a) criteria for the protection of human health. The changes contained in the bioaccumulation portion of the 2000 Human Health Methodology are mostly designed to:

- Improve the ability to incorporate chemical exposure from sediments and aquatic food webs in assessing bioaccumulation potential,

- Expand the ability to account for site-specific factors which affect bioaccumulation, and

- Incorporate new data and assessment tools into the bioaccumulation assessment process.

A summary of the key changes that have been incorporated into the bioaccumulation portion of the 2000 Human Health Methodology and appropriate comparisons to the1980 Methodology are provided below.

5.1.3.1 Overall Approach

The 1980 Methodology for deriving 304(a) criteria for the protection of human health emphasized the assessment of bioconcentration (uptake from water only) through the use of the BCF. Based on the 1980 Methodology, measured BCFs were usually determined from laboratory data unless field data demonstrated consistently higher or lower accumulation compared with laboratory data. In these cases, "field BCFs" (currently termed field-measured BAFs) were recommended for use. For lipophilic chemicals where lab or field-measured data were unavailable, EPA recommended predicting BCFs from the octanol-water partition coefficient and the following equation from Veith et al. (1979): "log BCF = (0.85 log K_{ow}) - 0.70".

The 2000 Human Health Methodology revisions contained in this chapter emphasize the measurement of bioaccumulation (uptake from water, sediment, and diet) through the use of the BAF. Consistent with the 1980 Methodology, measured data are preferred over predictive approaches for determining the BAF (i.e., field-measured BAFs are generally preferred over predicted BAFs). However, the 2000 Human Health Methodology contains additional methods for deriving a national BAF that were not available in 1980. The preference for using the BAF methods also differs depending on the type and properties of the chemical. For example, the BAF derivation procedure differs for each of three broadly defined chemical categories: (1) nonionic organic, (2) ionic organic, and (3) inorganic and organometallic chemicals. Furthermore, within the category of nonionic organic chemicals, different procedures are used to derive the BAF depending on a chemicals' hydrophobicity and extent of chemical metabolism that would be expected to occur in aquatic biota.

5.1.3.2 Lipid Normalization

In the 1980 Methodology, BCFs for lipophilic chemicals were normalized by the lipid fraction in the tissue of fish and shellfish used to determine the BCF. Lipid normalization enabled BCFs to be averaged across tissues and organisms. Once the average lipid-normalized BCF was determined, it was adjusted by the consumption-weighted lipid content of commonly consumed aquatic organisms in the United States to obtain an overall consumption-weighted BCF. A similar procedure has been retained in the 2000 Human Health Methodology, whereby BAFs for nonionic organic chemicals are lipid normalized and adjusted by the consumption-weighted lipid content of commonly consumed organisms to obtain a BAF for criteria

calculations. However, the 2000 Human Health Methodology uses more up-to-date lipid data and consumption data for deriving the consumption-weighted BAFs.

5.1.3.3 Bioavailability

Bioconcentration factors derived according to the 1980 Methodology were based on the total concentration of the chemical in water, for both lipophilic and nonlipophilic chemicals. In the 2000 Human Health Methodology, BAFs for nonionic organic chemicals are derived using the most bioavailable fraction (i.e., the freely dissolved fraction) to account for the influence of particulate and dissolved organic carbon on a chemical's bioavailability. Such BAFs are then adjusted to reflect the expected bioavailability at the sites of interest (i.e., by adjusting for organic carbon concentrations at the sites of interest). Procedures for accounting for the effect of organic carbon on bioaccumulation were published previously by EPA under the Great Lakes Water Quality Initiative (GLWQI or GLI) rulemaking (USEPA, 1995a,b). Bioavailability is also considered in developing BAFs for the other chemical classes defined in the 2000 Human Health Methodology (e.g., ionic organics, inorganics/organometallics) but is done so on a chemical-by-chemical basis.

5.1.3.4 Trophic Level Considerations

In the 1980 Methodology, BCFs were determined and used for criteria derivation without explicit regard to the trophic level of the aquatic organism (e.g., benthic filter feeder, forage fish, predatory fish). Over the past two decades, much information has been assembled which demonstrates that an organism's trophic position in the aquatic food web can have an important effect on the magnitude of bioaccumulation of certain chemicals. In order to account for the variation in bioaccumulation that is due to trophic position of the organism, the 2000 Human Health Methodology recommends that BAFs be determined and applied on a trophic level-specific basis.

5.1.3.5 Site-Specific Adjustments

The 1980 Methodology contained little guidance for making adjustments to the national BCFs to reflect site- or region-specific conditions. The 2000 Human Health Methodology has greatly expanded the guidance to States and authorized Tribes for making adjustments to national BAFs to reflect local conditions. This guidance is contained in the Bioaccumulation TSD. In the Bioaccumulation TSD, guidance and data are provided for adjusting national BAFs to reflect the lipid content in locally consumed aquatic biota and the organic carbon content in the waterbodies of concern. This guidance also allows the use of appropriate bioaccumulation models for deriving site-specific BAFs. EPA also plans to publish detailed guidance on designing and conducting field bioaccumulation studies for measuring BAFs and biota-sediment accumulation factors (BSAFs). In general, EPA encourages States and authorized Tribes to make site-specific modifications to EPA's national BAFs provided such adjustments are scientifically defensible and adequately protect the designated use of the waterbody.

While the aforementioned revisions are new to EPA's Methodology for deriving national 304(a) criteria for the protection of human health, many of these refinements have been

incorporated in prior Agency guidance and regulations. For example, the use of food chain multipliers to account for the biomagnification of nonionic organic chemicals in aquatic food webs when measured data are unavailable was introduced by EPA in three documents*: Technical Support Document for Water Quality-Based Toxics Control* (USEPA, 1991), a draft document entitled *Assessment and Control of Bioconcentratable Contaminants in Surface Waters* (USEPA, 1993), and in the *Great Lakes Water Quality Initiative* (GLI) (USEPA, 1995b). Similarly, procedures for predicting BAFs using BSAFsand incorporating the effect of organic carbon on bioavailability were used to derive water quality criteria under the GLI.

5.1.4 Organization of This Section

The methodology for deriving national BAFs for use in deriving National 304(a) Human Health AWQC is provided in the following sections. Important terms used throughout this chapter are defined in Section 5.2. Section 5.3 provides an overview of the BAF derivation guidelines. Detailed procedures for deriving national BAFs are provided in Section 5.4 for nonionic organic chemicals, in Section 5.5 for ionic organic chemicals, and in Section 5.6 for inorganics and organometallic chemicals. Literature cited is provided in Section 5.7.

5.2 DEFINITIONS

The following terms and definitions are used throughout this chapter.

Bioaccumulation. The net accumulation of a substance by an organism as a result of uptake from all environmental sources.

Bioconcentration. The net accumulation of a substance by an aquatic organism as a result of uptake directly from the ambient water, through gill membranes or other external body surfaces.

Bioaccumulation Factor (BAF). The ratio (in L/kg-tissue) of the concentration of a substance in tissue to its concentration in the ambient water, in situations where both the organism and its food are exposed and the ratio does not change substantially over time. The BAF is calculated as:

$$BAF = \frac{C_t}{C_w} \qquad \text{(Equation 5-2)}$$

where:

C_t = Concentration of the chemical in the specified wet tissue
C_w = Concentration of chemical in water

Bioconcentration Factor (BCF). The ratio (in L/kg-tissue) of the concentration of a substance in tissue of an aquatic organism to its concentration in the ambient water, in situations where the organism is exposed through the water only and the ratio does not change substantially over time. The BCF is calculated as:

$$BCF = \frac{C_t}{C_w} \qquad \text{(Equation 5-3)}$$

where:

C_t = Concentration of the chemical in the specified wet tissue
C_w = Concentration of chemical in water

Baseline BAF (BAF_ℓ^{fd}). For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), a BAF (in L/kg-lipid) that is based on the concentration of freely dissolved chemical in the ambient water and the lipid normalized concentration in tissue.

Baseline BCF (BCF_ℓ^{fd}). For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), a BCF (in L/kg-lipid) that is based on the concentration of freely dissolved chemical in the ambient water and the lipid normalized concentration in tissue.

Biomagnification. The increase in tissue concentration of a chemical in organisms at successive trophic levels through a series of predator-prey associations, primarily through the mechanism of dietary accumulation.

Biomagnification Factor (BMF). The ratio (unitless) of the tissue concentration of a chemical in a predator at a particular trophic level to the tissue concentration in its prey at the next lower trophic level for a given waterbody and chemical exposure. For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), a BMF can be calculated using lipid-normalized concentrations in the tissue of organisms at two successive trophic levels as:

$$BMF_{(TL,\ n)} = \frac{C_{\ell\ (TL,\ n)}}{C_{\ell\ (TL,\ n-1)}} \qquad \text{(Equation 5-4)}$$

where:

$C_{\ell\ (TL,\ n)}$ = Lipid-normalized concentration in appropriate tissue of predator organism at a given trophic level (TL “n”)

$C_{\ell\ (TL,\ n-1)}$ = Lipid-normalized concentration in appropriate tissue of prey organism at the next lower trophic level from the predator (TL "n-1")

For inorganic, organometallic, and certain ionic organic chemicals where lipid and organic carbon partitioning does not apply, a BMF can be calculated using chemical concentrations in the tissue of organisms at two successive trophic levels as:

$$BMF_{(TL,\ n)} = \frac{C_{t\ (TL,\ n)}}{C_{t\ (TL,\ n-1)}} \qquad \text{(Equation 5-5)}$$

where:

$C_{t\ (TL,\ n)}$ = Concentration in appropriate tissue of predator organism at trophic level "n" (may be either wet weight or dry weight concentration so long as both the predator and prey concentrations are expressed in the same manner)

$C_{t\ (TL,\ n-1)}$ = Concentration in appropriate tissue of prey organism at the next lower trophic level from the predator (may be either wet weight or dry weight concentration so long as both the predator and prey concentrations are expressed in the same manner)

Biota-Sediment Accumulation Factor (BSAF). For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), the ratio of the lipid-normalized concentration of a substance in tissue of an aquatic organism to its organic carbon-normalized concentration in surface sediment (expressed as kg of sediment organic carbon per kg of lipid), in situations where the ratio does not change substantially over time, both the organism and its food are exposed, and the surface sediment is representative of average surface sediment in the vicinity of the organism. The BSAF is defined as:

$$BSAF = \frac{C_{\ell}}{C_{soc}} \qquad \text{(Equation 5-6)}$$

where:

C_{ℓ} = The lipid-normalized concentration of the chemical in tissues of the biota (µg/g lipid)

C_{soc} = The organic carbon-normalized concentration of the chemical in the surface sediment (µg/g sediment organic carbon)

Depuration. The loss of a substance from an organism as a result of any active or passive process.

Food Chain Multiplier (FCM). For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), the ratio of a baseline BAF_{ℓ}^{fd} for an organism of a particular trophic level to the baseline BCF_{ℓ}^{fd} (usually determined for organisms in trophic level one). For inorganic, organometallic, and certain ionic organic chemicals where lipid and organic carbon partitioning does not apply, a FCM is based on total (wet or dry weight) concentrations of the chemical in tissue.

Freely Dissolved Concentration. For nonionic organic chemicals, the concentration of the chemical that is dissolved in ambient water, excluding the portion sorbed onto particulate or dissolved organic carbon. The freely dissolved concentration is considered to represent the most bioavailable form of an organic chemical in water and, thus, is the form that best predicts bioaccumulation. The freely dissolved concentration can be determined as:

$$C_w^{fd} = (C_w^t) \cdot (f_{fd}) \qquad \text{(Equation 5-7)}$$

where:

C_w^{fd}	=	Freely dissolved concentration of the organic chemical in ambient water
C_w^t	=	Total concentration of the organic chemical in ambient water
f_{fd}	=	Fraction of the total chemical in ambient water that is freely dissolved

Hydrophilic. A term that refers to the extent to which a chemical is attracted to partitioning into the water phase. Hydrophilic organic chemicals have a greater tendency to partition into polar phases (e.g., water) compared to chemicals of hydrophobic chemicals.

Hydrophobic. A term that refers to the extent to which a chemical avoids partitioning into the water phase. Highly hydrophobic organic chemicals have a greater tendency to partition into nonpolar phases (e.g., lipid, organic carbon) compared with chemicals of lower hydrophobicity.

Lipid-normalized Concentration (C_{ℓ}). The total concentration of a contaminant in a tissue or whole organism divided by the lipid fraction in that tissue or whole organism. The lipid-normalized concentration can be calculated as:

$$C_{\ell} = \frac{C_t}{f_{\ell}} \qquad \text{(Equation 5-8)}$$

where:

C_t	=	Concentration of the chemical in the wet tissue (either whole organism or specified tissue)

f_ℓ = Fraction lipid content in the organism or specified tissue

Octanol-water Partition Coefficient (K_{ow}). The ratio of the concentration of a substance in the n-octanol phase to its concentration in the aqueous phase in an equilibrated two-phase octanol-water system. For log K_{ow}, the log of the octanol-water partition coefficient is a base 10 logarithm.

Organic Carbon-normalized Concentration (C_{soc}). For sediments, the total concentration of a contaminant in sediment divided by the fraction of organic carbon in sediment. The organic carbon-normalized concentration can be calculated as:

$$C_{soc} = \frac{C_s}{f_{oc}} \qquad \text{(Equation 5-9)}$$

where:

C_s = Concentration of chemical in sediment
f_{oc} = Fraction organic carbon in sediment

Uptake. Acquisition by an organism of a substance from the environment as a result of any active or passive process.

5.3 FRAMEWORK FOR DETERMINING NATIONAL BIOACCUMULATION FACTORS

5.3.1 Four Different Methods

Bioaccumulation factors used to derive national BAFs can be measured or predicted using some or all of the following four methods, depending on the type of chemical and its properties. These methods are:

(1) a measured BAF obtained from a field study (i.e., a field-measured BAF);

(2) a BAF predicted from a field-measured BSAF;

(3) a BAF predicted from a laboratory-measured BCF (with or without adjustment by an FCM); and

(4) a BAF predicted from a chemical's octanol-water partition coefficient (K_{ow}), with or without adjustment using an FCM.

A brief summary of each of the four methods is provided below. Additional details on the use of these four methods is provided in Section 5.4 (for nonionic organics), Section 5.5 (for ionic organics) and Section 5.6 (for inorganics and organometallics).

1. **Field-Measured BAF.** Use of a field-measured BAF, which is the most direct measure of bioaccumulation, is the only method that can be used to derive a national BAF for all types of chemicals (i.e., nonionic organic, ionic organic, and inorganic and organometallic chemicals). A field-measured BAF is determined from a field study using measured chemical concentrations in the aquatic organism and its surrounding water. Because field studies are conducted in natural aquatic ecosystems, a field-measured BAF reflects an organism's exposure to a chemical through all relevant exposure pathways (i.e., water, sediment, and diet). A field-measured BAF also reflects any metabolism of a chemical that might occur in the aquatic organism or its food web. Therefore, field-measured BAFs are appropriate for all chemicals, regardless of the extent of chemical metabolism in biota.

2. **Field-measured BSAF.** For nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies), a BAF can also be predicted from BSAFs. A BSAF is similar to a field-measured BAF in that the concentration of a chemical in biota is measured in the field and reflects an organism's exposure to all relevant exposure routes. A BSAF also reflects any chemical metabolism that might occur in the aquatic organism or its food web. However, unlike a field-measured BAF which references the biota concentration to the water concentration, a BSAF references the biota concentration to the sediment concentration. Use of the BSAF procedure is restricted to organic chemicals which are classified as being moderately to highly hydrophobic.

3. **Lab-measured BCF.** A laboratory-measured BCF can also be used to estimate a BAF for organic and inorganic chemicals. However, unlike a field-measured BAF or a BAF predicted from a field-measured BSAF, a laboratory-measured BCF only reflects the accumulation of chemical through the water exposure route. Laboratory-measured BCFs may therefore under estimate BAFs for chemicals where accumulation from sediment or dietary sources is important. In these cases, laboratory-measured BCFs can be multiplied by a FCM to reflect accumulation from non-aqueous (i.e., food chain) pathways of exposure. Since a laboratory-measured BCF is determined using the measured concentration of a chemical in an aquatic organism and its surrounding water, a laboratory-measured BCF reflects any metabolism of the chemical that occurs in the organism, but not in the food web.

4. **K_{ow}.** A chemical's octanol-water partition coefficient, or K_{ow}, can also be used to predict a BAF for nonionic organic chemicals. This procedure is appropriate only for nonionic organic chemicals (and certain ionic organic chemicals where similar lipid and organic carbon partitioning behavior applies). The K_{ow} has been extensively correlated with the BCF for nonionic organic chemicals that are poorly metabolized by aquatic organisms. Therefore, where substantial metabolism is known to occur in biota, the K_{ow} is not used

to predict the BAF. For nonionic organic chemicals where chemical exposure through the food web is important, use of the K_{ow} alone will under predict the BAF. In such cases, the K_{ow} is adjusted with a FCM similar to the BCF procedure above.

5.3.2 Overview of BAF Derivation Framework

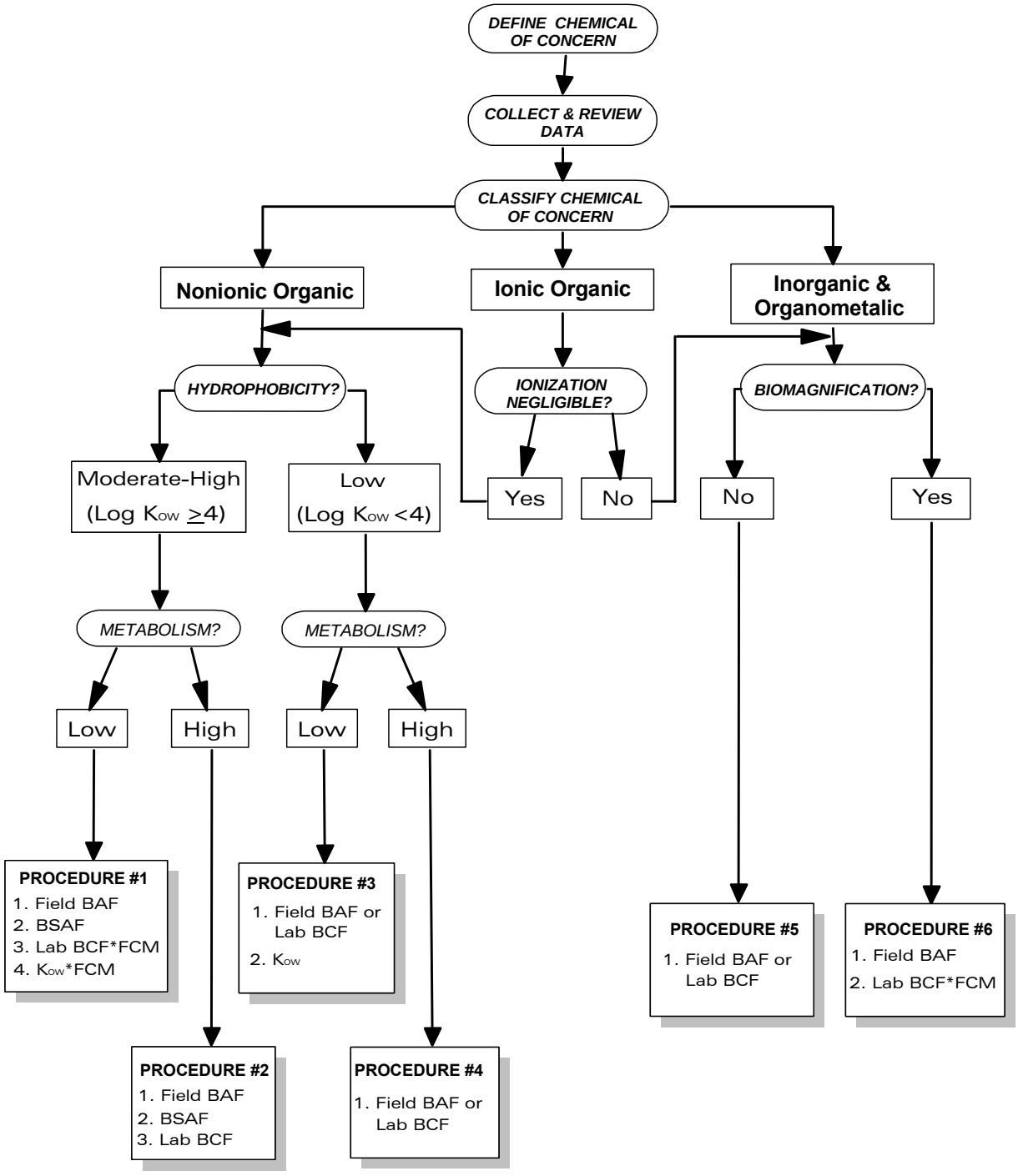
Although up to four methods can be used to derive a BAF as described in the previous section, it is evident that these methods do not apply equally to all types of chemicals. In addition, experience demonstrates that the required data will usually not be available to derive a BAF value using all of the applicable methods. As a result, EPA has developed the following guidelines to direct users in selecting the most appropriate method(s) for deriving a national BAF.

Figure 5-1 shows the overall framework of EPA's national BAF methodology. This framework illustrates the major steps and decisions that will ultimately lead to calculating a national BAF using one of six hierarchical procedures shown at the bottom of Figure 5-1. Each procedure contains a hierarchy of the BAF derivation methods discussed above, the composition of which depends on the chemical type and certain chemical properties (e.g., its degree of hydrophobicity and expected degree of metabolism and biomagnification). The number assigned to each BAF method within a procedure indicates its general order of preference for deriving a national BAF value. The goal of the framework and accompanying guidelines is to enable full use of available data and methods for deriving a national BAF value while appropriately restricting the use of certain methods to reflect their inherent limitations.

The first step in the framework is to define the chemical of concern. As described in Section 5.3.3, the chemical used to derive the national BAF should be consistent with the chemical used to derive the critical health assessment value. The second step is to collect and review all relevant data on bioconcentration and bioaccumulation of the chemical of concern (see Section 5.3.4). Once pertinent data are reviewed, the third step is to classify the chemical of concern into one of three broadly defined chemical categories: (1) nonionic organic chemicals, (2) ionic organic chemicals, and (3) and inorganic and organometallic chemicals. Guidance for classifying chemicals into these three categories is provided in Section 5.3.5.

After a chemical has been classified into one of the three categories, other information is used to select one of six hierarchical procedures to derive the national BAF. The specific procedures for deriving a BAF for each chemical group are discussed in Section 5.4 for nonionic organics, Section 5.5 for ionic organics, and Section 5.6 for inorganics and organometallics.

Figure 5-1. Framework for Deriving a National BAF



Detailed guidance concerning the first three steps of the derivation process (i.e, defining the chemical of concern, collecting and reviewing data, and classifying the chemical of concern) is provided in the following three sections.

5.3.3 Defining the Chemical of Concern

Defining the chemical of concern is the first step in deriving a national BAF. This step involves precisely defining the form(s) of the chemical upon which the national BAF value will be derived. Although this step is usually straightforward for single chemicals, complications can arise when the chemical of concern occurs as a mixture. The following guidelines should be followed for defining the chemical of concern.

1. Information for defining the chemical of concern should be obtained from the health and exposure assessment portions of the criteria derivation effort. The chemical(s) used to derive the national BAF should be consistent with the chemical(s) used to derive the reference dose (RfD), point of departure/uncertainty factor (POD/UF), or cancer potency factor.

2. In most cases, the RfD, POD/UF, or cancer potency factor will be based on a single chemical. In some cases, the RfD, POD/UF, or cancer potency factor will be based on a mixture of compounds, typically within the same chemical class (e.g., toxaphene, chlordane). In these situations, the national BAF should be derived in a manner that is consistent with the mixture used to express the health assessment.

    a. If sufficient data are available to reliably assess the bioaccumulation of each relevant compound contained in the mixture, then the national BAF(s) should be derived using the BAFs for the individual compounds of the mixture and appropriately weighted to reflect the mixture composition used to establish the RfD, POD/UF, or cancer potency factor. An example of this approach is shown in the derivation of BAFs for PCBs in the GLI Rulemaking (USEPA, 1997).

    b. If sufficient data are not available to reliably assess the bioaccumulation of individual compounds of the mixture, then the national BAF(s) should be derived using BAFs for the same or appropriately similar chemical mixture as that used to establish the RfD, POD/UF, or cancer potency value.

5.3.4 Collecting and Reviewing Data

The second step in deriving a national BAF is to collect and review all relevant bioaccumulation data for the chemical of concern. The following guidance should be followed for collecting and reviewing bioaccumulation data for deriving national BAFs.

1. All data on the occurrence and accumulation of the chemical of concern in aquatic animals and plants should be collected and reviewed for adequacy.

2. A comprehensive literature search strategy should be used for gathering bioaccumulation-related data. An example of a comprehensive literature search strategy is provided in the Bioaccumulation TSD.

3. All data that are used should contain sufficient supporting information to indicate that acceptable measurement procedures were used and that the results are probably reliable. In some cases it may be appropriate to obtain additional written information from the investigator.

4. Questionable data, whether published or unpublished, should not be used. Guidance for assessing the acceptability of bioaccumulation and bioconcentration studies is found in Sections 5.4, 5.5, and 5.6.

5.3.5 Classifying the Chemical of Concern

The next step in deriving a national BAF consists of classifying the chemical of concern into one of three categories: nonionic organic, ionic organic, and inorganic and organometallic (Figure 5-1). This step helps to determine which of the four methods described in Section 5.3.1 are appropriate for deriving BAFs. The following guidance applies for classifying the chemical of concern.

1. **Nonionic Organic Chemicals.** For the purposes of the 2000 Human Health Methodology, nonionic organic chemicals are those organic compounds that do not ionize substantially in natural bodies of water. These chemicals are also referred to as neutral or nonpolar organics in the scientific literature. Due to their neutrality, nonionic organic chemicals tend to associate with other neutral (or near neutral) compartments in aquatic ecosystems (e.g., lipid, organic carbon). Examples of nonionic organic chemicals which have been widely studied in terms of their bioaccumulation include polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins and furans, many chlorinated pesticides, and polynuclear aromatic hydrocarbons (PAHs). Procedures for deriving a national BAF for nonionic organic chemicals are provided in Section 5.4.

2. **Ionic Organic Chemicals.** For the purposes of the 2000 Human Health Methodology, ionic organic chemicals are considered to include those chemicals that contain functional groups with exchangeable protons such as hydroxyl, carboxylic, and sulfonic groups and functional groups that readily accept protons such as amino and aromatic heterocyclic nitrogen (pyridine) groups. Ionic organic chemicals undergo ionization in water, the extent of which depends on pH and the pKa of the chemical. Because the ionized species of these chemicals behave differently from the neutral species, separate guidance is provided for deriving BAFs for ionic organic chemicals. Procedures for deriving national BAFs for ionic organic chemicals are provided in Section 5.5.

3. **Inorganic and Organometallic Chemicals.** The inorganic and organometallic category is considered to include inorganic minerals, other inorganic compounds and elements, metals (e.g., copper, cadmium, chromium, zinc), metalloids (selenium, arsenic) and

organometallic compounds (e.g., methylmercury, tributyltin, tetraalkyllead). Procedures for deriving BAFs for inorganic and organometallic chemicals are provided in Section 5.6.

5.4 NATIONAL BIOACCUMULATION FACTORS FOR NONIONIC ORGANIC CHEMICALS

5.4.1 Overview

This section contains the methodology for deriving national BAFs for nonionic organic chemicals as defined in Section 5.3.5. The four general steps of this methodology are:

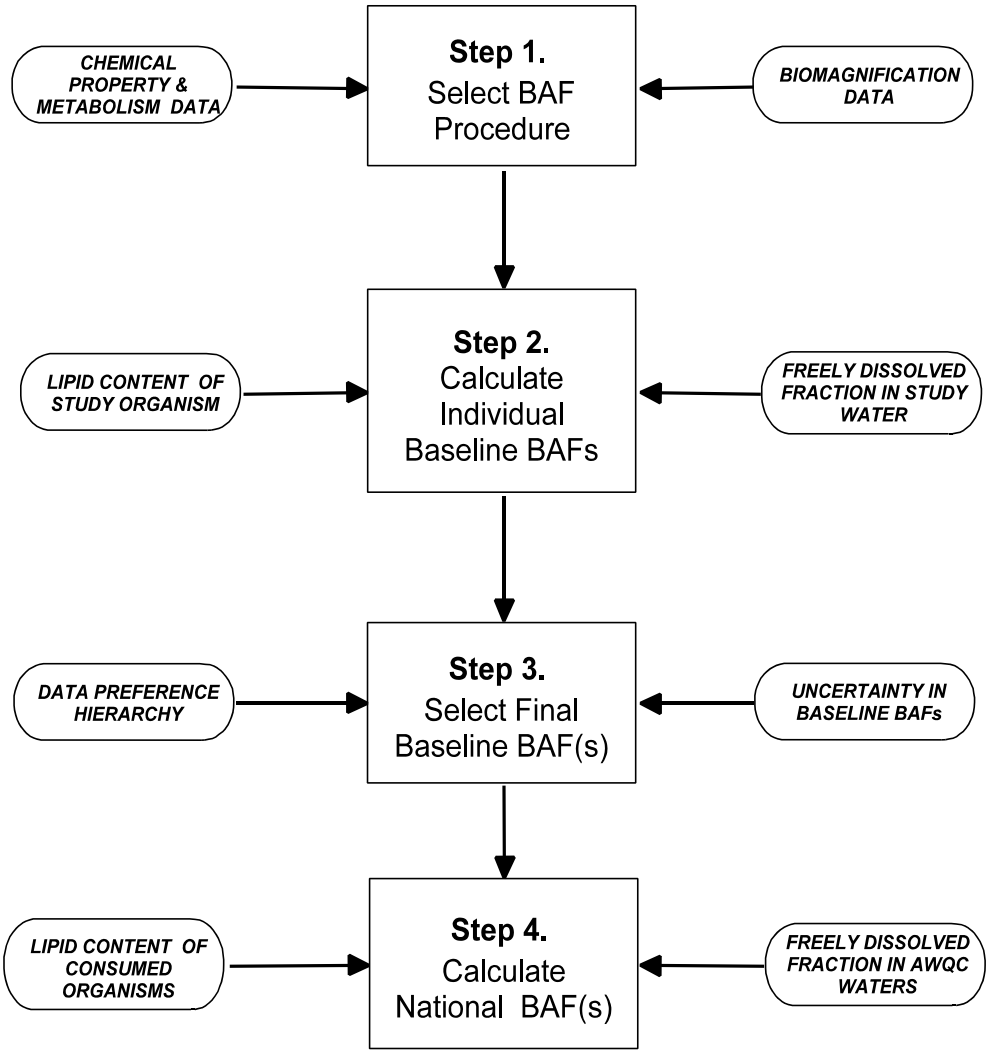
1. Selecting the BAF derivation procedure,
2. Calculating individual baseline BAF_{ℓ}^{fd}s,
3. Selecting the final baseline BAF_{ℓ}^{fd}s, and
4. Calculating the national BAFs from the final baseline BAF_{ℓ}^{fd}s.

A schematic of this four-step process is shown in Figure 5-2.

Step 1 of the methodology (selecting the BAF derivation procedure) determines which of the four BAF procedures summarized in Figure 5-1 will be appropriate for deriving the national BAF. Step 2 involves calculating individual, species-specific BAF_{ℓ}^{fd}s using all of the methods available within the selected BAF derivation procedure. Calculating the individual baseline BAF_{ℓ}^{fd}s involves using data from the field site or laboratory where the original data were collected to account for site-specific factors which affect the bioavailability of the chemical to aquatic organisms (e.g., lipid content of study organisms and freely dissolved concentration in study water). Step 3 of the methodology consists of selecting the final baseline BAF_{ℓ}^{fd}s from the individual baseline BAF_{ℓ}^{fd}s by taking into account the uncertainty in the individual BAFs and the data preference hierarchy selected in Step 1. The final step is to calculate a BAF (or BAFs) that will be used in the derivation of 304(a) criteria (i.e., referred to as the national BAF). This step involves adjusting the final baseline BAF_{ℓ}^{fd}(s) to reflect certain factors that affect bioavailablity of the chemical to aquatic organisms in waters to which the national 304(a) criteria will apply (e.g., the freely dissolved fraction expected in U.S. waters and the lipid content of consumed aquatic organisms). Baseline BAF_{ℓ}^{fd}s are not used directly in the derivation of the 304(a) criteria because they do not reflect the conditions that affect bioavailability in U.S. waters.

Section 5.4.2 below provides detailed guidance for selecting the appropriate BAF derivation procedure (Step 1 of the process). Guidance on calculating individual baseline BAF_{ℓ}^{fd}s, selecting the final baseline BAF, and calculating the national BAF (Steps 2 through 4 of the process) is provided in separate sections under each of the four BAF derivation procedures.

Figure 5-2. BAF Derivation for Nonionic Organic Chemicals



5.4.2 Selecting the BAF Derivation Procedure

This section describes the decisions that should be made to select one of the four available hierarchical procedures for deriving a national BAF for nonionic organic chemicals (Procedures #1 through #4 of Figure 5-1). As shown in Figure 5-1, two decision points exist in selecting the BAF derivation procedure. The first decision point requires knowledge of the chemical's hydrophobicity (i.e., the K_{ow} of the chemical). Guidance for selecting the K_{ow} for a chemical is provided in the Bioaccumulation TSD. The K_{ow} provides an initial basis for assessing whether biomagnification may be a concern for nonionic organic chemicals. The second decision point is based on the rate of metabolism for the chemical in the target organism. Guidance for assessing whether a high or low rate of metabolism is likely for a chemical of concern is provided below in Section 5.4.2.3. With the appropriate information for these two decision points, the BAF derivation procedure should be selected using the following guidelines.

5.4.2.1 <u>Chemicals with Moderate to High Hydrophobicity</u>

1. For the purposes of the 2000 Human Health Methodology, nonionic organic chemicals with log K_{ow} values equal to or greater than 4.0 should be classified as moderately to highly hydrophobic. For moderately to highly hydrophobic nonionic organic chemicals, available data indicate that exposure through the diet and other non-aqueous routes can become important in determining chemical residues in aquatic organisms (e.g., Russell et al., 1999; Fisk et al., 1998; Oliver and Niimi, 1983; Oliver and Niimi, 1988; Niimi, 1985; Swackhammer and Hites, 1988). Dietary and other non-aqueous exposure can become extremely important for those nonionic organic chemicals that are poorly metabolized by aquatic biota (e.g., certain PCB congeners, chlorinated pesticides, and polychlorinated dibenzo-p-dioxins and furans).

2. **Procedure #1** should be used to derive national BAFs for moderately to highly hydrophobic nonionic organic chemicals in cases where:

   (a) the rate of chemical metabolism by target aquatic organisms is expected to be sufficiently low such that biomagnification is of concern, or

   (b) the rate of chemical metabolism by target aquatic organisms is not sufficiently known.

   Procedure #1 accounts for non-aqueous exposure and the potential for biomagnification in aquatic food webs through the use of field-measured values for bioaccumulation (i.e., field measured BAF or BSAF) and FCMs when appropriate field data are unavailable. Guidance on deriving national BAFs using Procedure #1 is found below in Section 5.4.3.

3. **Procedure #2** should be used to derive the national BAFs for moderately to highly hydrophobic nonionic organic chemicals in cases where:

   (a) the rate of chemical metabolism by target aquatic organisms is expected to be sufficiently high such that biomagnification is not of concern.

Procedure #2 relaxes the requirement of using FCMs and eliminates the use of K_{ow}-based estimates of the BAF, two procedures that are most appropriate for poorly metabolized nonionic organic chemicals. Guidance on deriving national BAFs using Procedure #2 is found below in Section 5.4.4.

5.4.2.2 Chemicals with Low Hydrophobicity

1. For the purposes of these guidelines, nonionic organic chemicals with log K_{ow} values less than 4.0 should be classified as exhibiting low hydrophobicity. For nonionic organic chemicals that exhibit low hydrophobicity (i.e., log $K_{ow} < 4.0$), available information indicates that non-aqueous exposure to these chemicals is not likely to be important in determining chemical residues in aquatic organisms (e.g., Fisk et al., 1998; Gobas et al., 1993; Connolly and Pedersen, 1988; Thomann, 1989). For this group of chemicals, laboratory-measured BCFs and K_{ow}-predicted BCFs do not require adjustment with FCMs for determining the national BAF (Procedures #3 and #4), unless other appropriate data indicate differently.

   Other appropriate data include studies clearly indicating that non-aqueous exposure is important such that use of a BCF would substantially underestimate residues in aquatic organisms. In these cases, Procedure #1 should be used to derive the BAF for nonionic organic chemicals with log $K_{ow} < 4.0$. Furthermore, the data supporting the K_{ow} determination should be carefully reviewed for accuracy and appropriate interpretation, since the apparent discrepancy may be due to errors in determining K_{ow}.

2. **Procedure #3** should be used to derive national BAFs for nonionic organic chemicals of low hydrophobicity in cases where:

   (a) the rate of chemical metabolism by target aquatic organisms is expected to be negligible, such that tissue residues of the chemical of concern are not substantially reduced compared to an assumption of no metabolism, or

   (b) the rate of chemical metabolism by target aquatic organisms is not sufficiently known.

   Procedure #3 includes the use of K_{ow}-based estimates of the BCF to be used when lab or field data are absent. Guidance on deriving national BAFs using Procedure #3 is found below in Section 5.4.5.

3. **Procedure #4** should be used to derive national BAFs for nonionic organic chemicals of low hydrophobicity in cases where:

   (a) the rate of chemical metabolism by target aquatic organisms is expected to be sufficiently high, such that tissue residues of the chemical of concern are substantially reduced compared with an assumption of no metabolism.

Procedure #4 eliminates the option of using K_{ow}-based estimates of the BAF because the K_{ow} may over-predict accumulation when a chemical is metabolized substantially by an aquatic organism. Guidance on deriving national BAFs using Procedure #4 is found below in Section 5.4.6.

5.4.2.3 Assessing Metabolism

Currently, assessing the degree to which a chemical is metabolized by aquatic organisms is confounded by a variety of factors. First, conclusive data on chemical metabolism in aquatic biota are largely lacking. Such data include whole organism studies where the metabolic rates and breakdown products are quantified in fish and other aquatic organisms relevant to human consumption. However, the majority of information on metabolism is derived from *in vitro* liver microsomal preparations in which primary and secondary metabolites may be identified and their rates of formation may or may not be quantified. Extrapolating results from *in vitro* studies to the whole organism involves considerable uncertainty. Second, there are no generally accepted procedures for reliably predicting chemical metabolism by aquatic organisms in the absence of measured data. Third, the rate at which a chemical is metabolized by aquatic organisms can be species and temperature dependent. For example, PAHs are known to be metabolized readily by vertebrate aquatic species (primarily fish), although at rates much less than those observed for mammals. However, the degree of metabolism in invertebrate species is generally much less than the degree in vertebrate species (James, 1989). One hypothesis for this difference is that the invertebrate species lack the detoxifying enzymes and pathways that are present in many vertebrate species.

Given the current limitations on assessing the degree of chemical metabolism by aquatic organisms, the assessment of metabolism should be made on a case-by-case basis using a weight-of-evidence approach. When assessing a chemical's likelihood to undergo substantial metabolism in a target aquatic organism, the following data should be carefully evaluated:

(1) *in vivo* chemical metabolism data,
(2) bioconcentration and bioaccumulation data,
(3) data on chemical occurrence in target aquatic biota, and
(4) *in vitro* chemical metabolism data.

1. ***In vivo* Data.** *In vivo* data on metabolism in aquatic organisms are from studies of chemical metabolism using whole organisms. These studies are usually conducted using large fish from which blood, bile, urine, and individual tissues can be collected for the identification and quantification of metabolites formed over time. *In vivo* studies are considered the most useful for evaluating a chemical's degree of metabolism in an organism because both oxidative (Phase I) and conjugative (Phase II) metabolism can be assessed in these studies. Mass-balance studies, in which parent compound elimination is quantified separately from biotransformation and elimination of metabolites, allow calculation of conversion rate of parent to metabolite as well as metabolite elimination. This information might be used to estimate loss due to metabolism separately from that due to elimination of the parent compound for adjustment of K_{ow}-predicted BAFs. However, due to the analytical and experimental challenges these studies pose, data of

this type are limited. Less rigorous *in vivo* metabolism studies might include the use of metabolic blockers to demonstrate the influence of metabolism on parent compound kinetics. However, caution should be used in interpretation of absolute rates from these data due to the lack of specificity of mammalian derived blockers in aquatic species (Miranda et al., 1998).

2. **Bioconcentration or Bioaccumulation Data.** Data on chemical bioconcentration or bioaccumulation in aquatic organisms can be used indirectly for assessing metabolism. This assessment involves comparing acceptable lab-measured BCFs or field-measured BAFs (after converting to baseline values using procedures below) with the chemical's predicted value based on K_{ow}. The theoretical basis of bioconcentration and bioaccumulation for nonionic organic chemicals indicates that a chemical's baseline BCF should be similar to its K_{ow}-predicted value if metabolism is not occurring or is minimal (see the Bioaccumulation TSD). This theory also indicates that baseline BAFs should be similar to or higher than the K_{ow} for poorly metabolized organic chemicals, with highly hydrophobic chemicals often exhibiting higher baseline BAFs than K_{ow} values. Thus, if a chemical's baseline BCF or BAF is substantially lower than its K_{ow}, this may be an indication that the chemical is being metabolized by the aquatic organism of concern. Note, however, that this difference may also indicate problems in the experimental design or analytical chemistry, and that it may be difficult to discern the difference.

3. **Chemical Occurrence Data.** Although by no means definitive, data on the occurrence of chemicals in aquatic biota (i.e., residue studies) may offer another useful line of evidence for evaluating a chemical's likelihood to undergo substantial metabolism. Such studies are most useful if they have been conducted repeatedly over time and over wide geographical areas. Such studies might indicate a chemical is poorly metabolized if data show that the chemical is being biomagnified in the aquatic food web (i.e., higher lipid-normalized residues in successive trophic levels). Conversely, such studies might indicate a chemical is being metabolized substantially if residue data show a decline in residues with increasing trophic level. Again, other reasons for increases or decreases in concentrations with increasing trophic level might exist and should be carefully evaluated (e.g., incorrect food web assumptions, differences in exposure concentrations).

4. ***In vitro* Data.** *In vitro* metabolism data include data from studies where specific sub-cellular fractions (e.g., microsomal, cytosolic), cells, or tissues from an organism are tested outside the body (i.e., in test-tubes, cell- or tissue-culture). Compared with *in vivo* studies of chemical metabolism in aquatic organisms, *in vitro* studies are much more plentiful in the literature, with the majority of studies characterizing oxidative (Phase I) reactions de-coupled from conjugative (Phase II) metabolism. Cell, tissue, or organ level *in vitro* studies are less common but provide a more complete assessment of metabolism. While such studies are particularly useful for identifying the pathways, rates of formation, and metabolites formed, as well as the enzymes involved and differences in the temperature dependence of metabolism across aquatic species, they suffer from uncertainty when results are extrapolated to the whole organism. This uncertainty results from the fact that dosimetry (i.e., delivery of the toxicant to, and removal of metabolite

from, the target tissue) cannot currently be adequately reproduced in the laboratory or easily modeled.

When assessing chemical metabolism using the above information, the following guidelines apply.

a. A finding of substantial metabolism should be supported by two or more lines of evidence identified using the data described above.

b. At least one of the lines of evidence should be supported by either *in vivo* metabolism data or acceptable bioconcentration or bioaccumulation data.

c. A finding of substantial metabolism in one organism should not be extrapolated to another organism or another group of organisms unless data indicate similar metabolic pathways exist (or are very likely to exist) in both organisms. *In vitro* data may be particularly useful in cross-species extrapolations.

d. Finally, in situations where sufficient data are not available to properly assess the likelihood of significant metabolism in aquatic biota of concern, the chemical should be assumed to undergo little or no metabolism. This assumptions reflects a policy decision by EPA to err on the side of public health protection when sufficient information on metabolism is lacking.

5.4.3 Deriving National BAFs Using Procedure #1

This section contains guidance for calculating national BAFs for nonionic organic chemicals using Procedure #1 shown in Figure 5-1. The types of nonionic organic chemicals for which Procedure #1 is most appropriate are those that are classified as moderately to highly hydrophobic and subject to low (or unknown) rates of metabolism by aquatic biota (see Section 5.4.2 above). Non-aqueous contaminant exposure and subsequent biomagnification in aquatic food webs are of concern for chemicals that are classified in this category. Some examples of nonionic organic chemicals for which Procedure #1 is considered appropriate include:

- tetra-, penta- & hexachlorobenzenes;
- PCBs;
- octachlorostyrene;
- hexachlorobutadiene;
- endrin, dieldrin, aldrin;
- mirex, photomirex;
- DDT, DDE, DDD; and
- heptachlor, chlordane, nonachlor.

Under Procedure #1, the following four methods may be used in deriving a national BAF:

- using a BAF from an acceptable field study (i.e., a field-measured BAF);
- predicting a BAF from an acceptable field-measured BSAF;

- predicting a BAF from an acceptable laboratory-measured BCF and FCM; and
- predicting a BAF from an acceptable K_{ow} and FCM.

As shown in Figure 5-2, once the derivation procedure has been selected, the next steps in deriving a national BAF for a given trophic level include: calculating individual baseline BAF_{ℓ}^{fd}s (step 2), selecting the final baseline BAF_{ℓ}^{fd} (step 3), and calculating the national BAF from the final baseline BAF_{ℓ}^{fd} (step 4). Each of these three steps is discussed separately below.

5.4.3.1 Calculating Individual Baseline BAF_{ℓ}^{fd}s

Calculating an individual baseline BAF_{ℓ}^{fd} involves normalizing the field-measured BAF_{T}^{t} (or laboratory-measured BCF_{T}^{t}) which are based on total concentrations in tissue and water by the lipid content of the study organisms and the freely dissolved concentration in the study water. Both the lipid content in the organism and the freely dissolved concentration (as influenced by organic carbon in water) have been shown to be important factors that influence the bioaccumulation of nonionic organic chemicals (e.g., Mackay, 1982; Connolly and Pederson, 1988; Thomann, 1989, Suffet et al., 1994). Therefore, baseline BAF_{ℓ}^{fd}s (which are expressed on a freely dissolved and lipid-normalized basis) are considered more amenable to extrapolating between different species and bodies of water compared to BAFs expressed using the total concentration in the tissue and water. Because bioaccumulation can be strongly influenced by the trophic position of aquatic organisms (either due to biomagnification or physiological differences), extrapolation of baseline BAF_{ℓ}^{fd}s should not be performed between species of different trophic levels.

1. For each species for which acceptable data are available, calculate all possible baseline BAF_{ℓ}^{fd}s using each of the four methods shown above for Procedure #1.

2. Individual baseline BAF_{ℓ}^{fd}s should be calculated from field-measured BAF_{T}^{t}s, field-measured BSAFs, laboratory BCF_{T}^{t}s, and the K_{ow} according to the following procedures.

A. Baseline BAF_{ℓ}^{fd}s from Field-Measured BAFs

A baseline BAF_{ℓ}^{fd} should be calculated from each field-measured BAF_{T}^{t} using information on the lipid fraction in the tissue of concern for the study organism and the fraction of the total chemical that is freely dissolved in the study water.

1. **Baseline BAF_{ℓ}^{fd} Equation.** For each acceptable field-measured BAF_{T}^{t}, calculate a baseline BAF_{ℓ}^{fd} using the following equation:

$$\text{Baseline } BAF_{\ell}^{fd} = \left[\frac{\text{Measured } BAF_{T}^{t}}{f_{fd}} - 1 \right] \left(\frac{1}{f_{\ell}} \right) \qquad \text{(Equation 5-10)}$$

where:

Baseline BAF_{ℓ}^{fd}	=	BAF expressed on a freely dissolved and lipid-normalized basis
Measured BAF_T^t	=	BAF based on total concentration in tissue and water
f_{ℓ}	=	Fraction of the tissue that is lipid
f_{fd}	=	Fraction of the total chemical that is freely dissolved in the ambient water

The technical basis of Equation 5-10 is provided in the Bioaccumulation TSD. Guidance for determining each component of Equation 5-10 is provided below.

2. **Determining the Measured BAF_T^t.** The field-measured BAF_T^t shown in Equation 5-10 should be calculated based on the total concentration of the chemical in the appropriate tissue of the aquatic organism and the total concentration of the chemical in ambient water at the site of sampling. The equation to derive a measured BAF_T^t is:

$$\text{Measured } BAF_T^t = \frac{C_t}{C_w} \qquad \text{(Equation 5-11)}$$

where:

C_t	=	Total concentration of the chemical in the specified wet tissue
C_w	=	Total concentration of chemical in water

The data used to calculate a field-measured BAF_T^t should be reviewed thoroughly to assess the quality of the data and the overall uncertainty in the BAF value. The following general criteria apply in determining the acceptability of field-measured BAFs that are being considered for deriving national BAFs using Procedure #1.

a. Aquatic organisms used to calculate a field-measured BAF_T^t should be representative of aquatic organisms that are commonly consumed in the United States. An aquatic organism that is not commonly consumed in the United States can be used to calculate an acceptable field-measured BAF_T^t provided that the organism is considered to be a reasonable surrogate for a commonly consumed organism. Information on the ecology, physiology, and biology of the organism should be reviewed when assessing whether an organism is a reasonable surrogate of a commonly consumed organism.

b. The trophic level of the study organism should be determined by taking into account its life stage, diet, size, and the food web structure at the study location. Information from the study site (or similar sites) is preferred when evaluating trophic status. If such information is lacking, general information for assessing trophic status of aquatic organisms can be found in USEPA (2000a,b,c).

c. The percent lipid of the tissue used to determine the field-measured BAF_T^t should be either measured or reliably estimated to permit lipid-normalization of the chemical's tissue concentration.

d. The study from which the field-measured BAF_T^t is derived should contain sufficient supporting information from which to determine that tissue and water samples were collected and analyzed using appropriate, sensitive, accurate, and precise analytical methods.

e. The site of the field study should not be so unique that the BAF cannot be reasonably extrapolated to other locations where the BAF and resulting criteria will apply.

f. The water concentration(s) used to derive the BAF should reflect the average exposure of the aquatic organism that corresponds to the concentration measured in its tissue of concern. For nonionic organic chemicals, greater temporal and spatial averaging of chemical concentrations is required as the K_{ow} increases. In addition, as variability in water concentrations increase, greater temporal and spatial averaging is also generally required. Greater spatial averaging is also generally required for more mobile organisms.

g. The concentrations of particulate organic carbon and dissolved organic carbon in the study water should be measured or reliably estimated.

EPA is currently developing guidance for designing and conducting field studies for determining field-measured BAF_T^ts, including recommendations for minimum data requirements. A more detailed discussion of factors that should be considered when determining field-measured BAF_T^ts is provided in the Bioaccumulation TSD.

3. **Determining the Fraction Freely Dissolved (f_{fd}).** As illustrated by Equation 5-10, the fraction of the nonionic organic chemical that is freely dissolved in the study water is required for calculating a baseline BAF_ℓ^{fd} from a field-measured BAF_T^t. The freely dissolved fraction is the portion of the nonionic organic chemical that is not bound to particulate organic carbon or dissolved organic carbon. Together, the concentration of a nonionic organic chemical that is freely dissolved, bound to dissolved organic carbon, and bound to particulate organic carbon constitute its total concentration in water. As discussed further in the Bioaccumulation TSD, the freely dissolved fraction of a chemical is considered to be the best expression of the bioavailable form of nonionic organic chemicals to aquatic organisms (e.g., Suffet et al., 1994; USEPA, 1995b). Because the fraction of a nonionic organic chemical that is freely dissolved may vary among different bodies of water as a result of differences in dissolved and particulate organic carbon in the water, the bioavailability of the total chemical concentration in water is expected to vary from one body of water to another. Therefore, BAFs which are based on the freely dissolved concentration in water (rather than the total concentration in water) are considered to be more reliable for extrapolating and aggregating BAFs among different bodies of water. Currently, availability of BAFs based on measured freely dissolved

concentrations is very limited, partly because of difficulties in analytically measuring the freely dissolved concentration. Thus, if a BAF based on the total water concentration is reported in a given study, the fraction of the chemical that is freely dissolved should be predicted using information on the organic carbon content in the study water.

a. **Equation for Determining the Freely Dissolved Fraction.** If reliable measured data are unavailable to directly determine the freely dissolved fraction of the chemical in water, the freely dissolved fraction should be estimated using the following equation.

$$f_{fd} = \frac{1}{[1 + (POC \cdot K_{ow}) + (DOC \cdot 0.08 \cdot K_{ow})]} \qquad \text{(Equation 5-12)}$$

where:

POC	=	concentration of particulate organic carbon (kg/L)
DOC	=	concentration of dissolved organic carbon (kg/L)
K_{ow}	=	n-octanol water partition coefficient for the chemical

In Equation 5-12, K_{ow} is being used to estimate the partition coefficient to POC (i.e., K_{POC} in L/kg) and $0.08 \cdot K_{ow}$ is being used to estimate the partition coefficient to DOC (i.e., the K_{DOC} in L/kg). A discussion of the technical basis, assumptions, and uncertainty associated with the derivation and application of Equation 5-12 is provided in the Bioaccumulation TSD.

b. **POC and DOC Values.** When converting from the total concentration of a chemical to a freely dissolved concentration using Equation 5-12 above, the POC and DOC concentrations should be obtained from the original study from which the field-measured BAF is determined. If POC and DOC concentrations are not reported in the BAF study, reliable estimates of POC and DOC might be obtained from other studies of the same site used in the BAF study or closely related site(s) within the same water body. When using POC/DOC data from other studies of the same water body, care should be taken to ensure that environmental and hydrological conditions that might affect POC or DOC concentrations (i.e., runoff events, proximity to ground water or surface water inputs, sampling season) are reasonably similar to those in the BAF study. Additional information related to selecting POC and DOC values is provided in the Bioaccumulation TSD.

In some cases, BAFs are reported using the concentration of the chemical in filtered or centrifuged water. When converting these BAFs to a freely dissolved basis, the concentration of POC should be set equal to zero when using Equation 5-12. Particulates are removed from water samples by filtering or centrifuging the sample.

c. **Selecting K_{ow} Values.** A variety of techniques are available to measure or predict K_{ow} values. The reliability of these techniques depends to a large extent on the K_{ow} of the chemical. Because K_{ow} is an important input parameter for calculating the freely dissolved concentration of nonionic organic chemicals and for deriving BAFs using the other three methods of Procedure #1, care should be taken in selecting the most reliable K_{ow} value. The value of K_{ow} for use in estimating the freely dissolved fraction and other procedures used to derive national BAFs should be selected based on the guidance presented in the Bioaccumulation TSD.

4. **Determining the Fraction Lipid (f_ℓ).** Calculating a baseline BAF_ℓ^{fd} for a nonionic organic chemical using Equation 5-10 also requires that the total chemical concentration measured in the tissue used to determine the field-measured BAF_T^t be normalized by the lipid fraction (f_ℓ) in that same tissue. Lipid normalization of tissue concentrations reflects the assumption that BAFs (and BCFs) for nonionic organic chemicals are directly proportional to the percent lipid in the tissue upon which they are based. This assumption means that an organism with a two percent lipid content would be expected to accumulate twice the amount of a chemical at steady state compared with an organism with one percent lipid content, all else being equal. The assumption that aquatic organisms accumulate nonionic organic chemicals in proportion to their lipid content has been extensively evaluated in the literature (Mackay, 1982; Connell, 1988; Barron, 1990) and is generally accepted. Because the lipid content in aquatic organisms can vary both within and across species, BAFs that are expressed using the lipid-normalized concentration (rather than the total concentration in tissue) are considered to be the most reliable for aggregating multiple BAF values for a given species. Additional discussion of technical basis, assumptions, and uncertainties involved in lipid normalization is provided in the Bioaccumulation TSD.

a. The lipid fraction f_ℓ, is routinely reported in bioaccumulation studies involving nonionic organic chemicals. If the lipid fraction is not reported in the BAF study, it can be calculated using the following equation if the appropriate data are reported:

$$f_\ell = \frac{M_\ell}{M_t} \qquad \text{(Equation 5-13)}$$

where:

M_ℓ = Mass of lipid in specified tissue
M_t = Mass of specified tissue (wet weight)

b. Because lipid content can vary within an aquatic organism (and among tissues within that organism) due to several factors including the age and sex of the organism, changes in dietary composition, season of sampling and reproductive status, the lipid fraction used to calculate a baseline BAF_ℓ^{fd} should be measured in

the same tissue and organisms used to determine the field-measured BAF_T^t, unless comparability is demonstrated across organisms.

c. Experience has shown that different solvent systems used to extract lipids for analytical measurement can result in different quantities of lipids being extracted and measured in aquatic organisms (e.g., Randall et al.,1991, 1998). As a result, lipid measurements determined using different solvent systems might lead to apparent differences in lipid-normalized concentrations and lipid-normalized BAFs. The extent to which different solvent systems might affect lipid extractions (and lipid-normalized concentrations) is thought to vary depending on the solvent, chemical of concern, and lipid composition of the tissue being extracted. Guidance on measurement of lipid content, including the choice of solvent system and how different solvent systems may affect lipid content, is provided in the Bioaccumulation TSD.

B. Baseline BAF_ℓ^{fd} Derived from BSAFs

The second method of determining a baseline BAF_ℓ^{fd} for the chemical of concern in Procedure #1 involves the use of BSAFs. Although BSAFs may be used for measuring and predicting bioaccumulation directly from concentrations of chemicals in surface sediment, they may also be used to estimate BAFs (USEPA, 1995b; Cook and Burkhard, 1998). Since BSAFs are based on field data and incorporate effects of chemical bioavailability, food web structure, metabolism, biomagnification, growth, and other factors, BAFs estimated from BSAFs will incorporate the net effect of all these factors. The BSAF approach is particularly beneficial for developing water quality criteria for chemicals which are detectable in fish tissues and sediments, but are difficult to detect or measure precisely in the water column.

As shown by Equation 5-14 below, predicting baseline BAF_ℓ^{fd}s using BSAFs requires that certain types of data be used for the chemicals of interest (for which BAFs are to be determined) and reference chemicals (for which BAFs are measured) from a common sediment-water-organism data set. Differences between BSAFs for different organic chemicals are good measures of the relative bioaccumulation potentials of the chemicals. When calculated from a common organism-sediment sample set, chemical-specific differences in BSAFs reflect the net effect of biomagnification, metabolism, food chain, bioenergetics, and bioavailability factors on the degree of each chemical's equilibrium/disequilibrium between sediment and biota. At equilibrium, BSAFs are expected to be approximately 1.0. However, deviations from 1.0 (reflecting disequilibrium) are common due to: conditions where water is not at equilibrium with surface sediment; differences in organic carbon content of water and sediment; kinetic limitations for chemical transfer between sediments and water associated with specific biota; biomagnification; or biological processes such as growth or biotransformation. BSAFs are most useful (i.e., most predictable from one site to another) when measured under steady-state (or near steady-state) conditions. The use of non-steady-state BSAFs, such as found with new chemical loadings or rapid increases in loadings, increases uncertainty in this method for the relative degree of disequilibrium between the reference chemicals and the chemicals of interest. In general, the fact that concentrations of hydrophobic chemicals in sediment are less sensitive than concentrations in water to fluctuations in chemical loading and distribution makes the BSAF

method robust for estimating BAFs. Results from validation of the BAF procedure in Lake Ontario, the Fox River and Green Bay, Wisconsin, and the Hudson River, New York, demonstrate good agreement between observed and BSAF-predicted BAFs in the vast majority of comparisons made. Detailed results of the validation studies for the BSAF procedure are provided in the Bioaccumulation TSD.

Baseline BAF_{ℓ}^{fd}s should be calculated using acceptable BSAFs for chemicals of interest and appropriate sediment-to-water fugacity (disequilibrium) ratios $(\prod_{socw})_r/(K_{ow})_r$ for reference chemicals under the following guidelines.

1. **Baseline BAF_{ℓ}^{fd} Equation.** For each species with an acceptable field measured $(BSAF)_I$, a baseline BAF_{ℓ}^{fd} for the chemical of interest may be calculated using the following equation with an appropriate value of $(\prod_{socw})_r/(K_{ow})_r$:

$$(Baseline\ BAF_{\ell}^{fd})_i = (BSAF)_i \frac{(D_{i/r})\ (\prod_{socw})_r\ (K_{ow})_i}{(K_{ow})_r} \qquad \text{(Equation 5-14)}$$

where:

$(\text{Baseline } BAF_{\ell}^{fd})_I$	=	BAF expressed on a freely dissolved and lipid-normalized basis for chemical of interest "I"
$(BSAF)_I$	=	Biota-sediment accumulation factor for chemical of interest "I"
$(\prod_{socw})_r$	=	sediment organic carbon to water freely dissolved concentration ratio of reference chemical "r"
$(K_{ow})_I$	=	octanol-water partition coefficient for chemical of interest "I"
$(K_{ow})_r$	=	octanol-water partition coefficient for the reference chemical "r"
$D_{i/r}$	=	ratio between $\prod_{socw}/K_{ow}$ for chemicals "I" and "r" (normally chosen so that $D_{i/r} = 1$)

The technical basis, assumptions, and uncertainties associated with Equation 5-14 are provided in the Bioaccumulation TSD. Guidance for determining each component of Equation 5-14 is provided below.

2. **Determining Field-Measured BSAFs.** BSAFs should be determined by relating lipid-normalized concentrations of chemicals in an organism (C_{ℓ}) to organic carbon-normalized concentrations of the chemicals in surface sediment samples (C_{soc}) using the following equation:

$$BSAF = \frac{C_{\ell}}{C_{soc}} \qquad \text{(Equation 5-15)}$$

a. **Lipid-Normalized Concentration.** The lipid-normalized concentration of a chemical in an organism should be determined by:

$$C_{\ell} = \frac{C_t}{f_{\ell}} \qquad \text{(Equation 5-16)}$$

where:

C_t = Concentration of the chemical in the wet tissue (either whole organism or specified tissue) (µg/g)
f_{ℓ} = Fraction lipid content in the tissue

b. **Organic Carbon-Normalized Concentration.** The organic carbon-normalized concentration of a chemical in sediment should be determined by:

$$C_{soc} = \frac{C_s}{f_{oc}} \qquad \text{(Equation 5-17)}$$

where:

C_s = Concentration of chemical in sediment (µg/g sediment)
f_{oc} = Fraction organic carbon in sediment

The organic carbon-normalized concentrations of the chemicals in surface sediment samples should be associated with the average exposure environment of the organism.

3. **Sediment-to-Water Partition Coefficient** $(\prod_{socw})_r$. Sediment-to-water partition coefficients for reference chemicals should be determined by:

$$(\prod_{socw})_r = \frac{(C_{soc})_r}{(C_w^{fd})_r} \qquad \text{(Equation 5-18)}$$

where:

$(C_{soc})_r$ = Concentration of a reference chemical in sediment normalized to sediment organic carbon
$(C_w^{fd})_r$ = Concentration of the reference chemical freely dissolved in water

4. **Selecting Reference Chemicals.** Reference chemicals with $(\prod_{socw})$ / (K_{ow}) similar to that of the chemical of interest are preferred for this method. Theoretically, knowledge of the

difference between sediment-to-water fugacity ratios for two chemicals, "I" and "r" ($D_{i/r}$), could be used when reliable reference chemicals that meet the fugacity equivalence condition are not available. Similarity of $(\prod_{socw}) / (K_{ow})$ for two chemicals can be indicated on the basis of similar physical-chemical behavior in water (persistence, volatilization), similar mass loading histories, and similar concentration profiles in sediment cores.

Validation studies have demonstrated that choosing reference chemicals with well quantified concentrations in water is important because the uncertainty associated with measurement of barely detected chemicals is large (see the Bioaccumulation TSD). Similarity between K_{ow} values of the reference and target chemicals is generally desirable, although recent validation studies indicate that the accuracy of the method is not substantially decreased through use of reference chemicals with large differences in K_{ow}, as long as the chemicals are structurally similar and have similar persistence behavior in water and sediments.

5. The following data, procedural, and quality assurance requirements should be met for predicting baseline BAF_{ℓ}^{fd}s using field-measured BSAFs:

   a. Data on the reference chemicals and chemicals of interest should come from a common organism-water-sediment data set at a particular site.

   b. The chemicals of interest and reference chemicals should have similar physicochemical properties and persistence in water and sediment.

   c. The loadings history of the reference chemicals and chemicals of interest should be similar such that their expected sediment-water disequilibrium ratios $(\prod_{socw}/K_{ow})$ would not be expected to be substantially different (i.e., $D_{i/r} \sim 1$).

   d. The use of multiple reference chemicals is generally preferred for determining the value of $(\prod_{socw})_r$ so long as the concentrations are well quantified and the aforementioned conditions for selecting reference chemicals are met. In some cases, use of a single reference chemical may be necessary because of limited data.

   e. Samples of surface sediments (0-1 cm is ideal) should be from locations in which sediment is regularly deposited and is representative of average surface sediment in the vicinity of the organism.

   f. The K_{ow} value for the target and reference chemicals should be selected as described in the Bioaccumulation TSD.

   g. All other data quality and procedural guidelines described earlier for determining field-measured BAFs in Section 5.4.3.1(A) should be met.

Further details on the requirements for predicting BAFs from BSAF measurements, including the data, assumptions, and limitations of this approach are provided in the Bioaccumulation TSD.

C. Baseline BAF_{ℓ}^{fd} from a Laboratory-Measured BCF_T^t and FCM

The third method in Procedure #1 consists of using a laboratory-measured BCF_T^t (i.e., a BCF based on total concentrations in tissue and water) and FCMs to predict a baseline BAF_{ℓ}^{fd} for the chemical of concern. The BCF_T^t is used in conjunction with an FCM because non-aqueous routes of exposure and subsequent biomagnification is of concern for the types of chemicals applicable to Procedure #1. A laboratory-measured BCF inherently accounts for the effects of chemical metabolism that occurs in the organism used to calculate the BCF, but does not account for metabolism which may occur in other organisms of the aquatic food web.

1. **Baseline BAF_{ℓ}^{fd} Equation.** For each acceptable laboratory-measured BCF_T^t, calculate a baseline BAF_{ℓ}^{fd} using the following equation:

$$\text{Baseline } BAF_{\ell}^{fd} = (FCM) \cdot \left[\frac{\text{Measured } BCF_T^t}{f_{fd}} - 1 \right] \cdot \left(\frac{1}{f_{\ell}} \right) \qquad \text{(Equation 5-19)}$$

where:

Baseline BAF_{ℓ}^{fd}	=	BAF expressed on a freely dissolved and lipid-normalized basis
Measured BCF_T^t	=	BCF based on total concentration in tissue and water
f_{ℓ}	=	Fraction of the tissue that is lipid
f_{fd}	=	Fraction of the total chemical in the test water that is freely dissolved
FCM	=	The food chain multiplier either obtained from Table 5-1 by linear interpolation for the appropriate trophic level, or from appropriate field data

The technical basis for Equation 5-19 is provided in the Bioaccumulation TSD. Guidance for determining each component of Equation 5-19 is provided below.

2. **Determining the Measured BCF_T^t.** The laboratory-measured BCF_T^t shown in Equation 5-19 should be calculated using information on the total concentration of the chemical in the tissue of the organism and the total concentration of the chemical in the laboratory test water. The equation to derive a measured BCF_T^t is:

$$\text{Measured } BCF_T^t = \frac{C_t}{C_w} \qquad \text{(Equation 5-20)}$$

where:

C_t = Total concentration of the chemical in the specified wet tissue
C_w = Total concentration of chemical in the laboratory test water

The data used to calculate a laboratory-measured BCF_T^t should be reviewed thoroughly to assess the quality of the data and the overall uncertainty in the BCF value. The following general criteria apply in determining the acceptability of laboratory-measured BCF_T^t.

a. The test organism should not be diseased, unhealthy, or adversely affected by the concentration of the chemical because these attributes may alter accumulation of chemicals compared with healthy organisms.

b. The total concentration of the chemical in the water should be measured and should be relatively constant during the exposure period.

c. The organisms should be exposed to the chemical using a flow-through or renewal procedure.

d. The percent lipid of the tissue used to normalize the BCF_T^t should be either measured or reliably estimated to permit lipid normalization of chemical concentrations.

e. The concentrations of particulate organic carbon and dissolved organic carbon in the study water should be measured or reliably estimated.

f. Aquatic organisms used to calculate a laboratory-measured BCF_T^t should be representative of those aquatic organisms that are commonly consumed in the United States. An aquatic organism which is not commonly consumed in the United States can be used to calculate an acceptable laboratory-measured BCF_T^t provided that the organism is considered to be a reasonable surrogate for a commonly consumed organism. Information on the ecology, physiology, and biology of the organism should be reviewed when assessing whether an organism is a reasonable surrogate of a commonly consumed organism.

g. BCFs may be based on measurement of radioactivity from radiolabeled parent compounds only when the BCF is intended to include metabolites, when there is confidence that there is no interference due to metabolites of the parent compounds, or when studies are conducted to determine the extent of metabolism, thus allowing for a proper correction.

h. The calculation of the BCF_T^t should appropriately address growth dilution, which can be particularly important in affecting BCF_T^t determinations for poorly depurated chemicals.

I. Other aspects of the methodology used should be similar to those described by the American Society of Testing and Materials (ASTM, 1999) and USEPA *Ecological Effects Test Guidelines* (USEPA, 1996).

j. In addition, the magnitude of the K_{ow} and the availability of corroborating BCF data should be considered. For example, if the steady-state method is used for the BCF_T^t determination, exposure periods longer than 28 days will generally be required for highly hydrophobic chemicals to reach steady state between the water and the organism.

k. If a baseline BCF_ℓ^{fd} derived from a laboratory-measured BCF_T^t consistently increases or decreases as the chemical concentration increases in the test solutions for the test organisms, the BCF_T^t should be selected from the test concentration(s) that would most closely correspond to the 304(a) criterion. Note: a BCF_T^t should not be calculated from a control treatment.

3. **Selecting Food Chain Multipliers.** An FCM reflects a chemical's tendency to biomagnify in the aquatic food web. Values of FCMs greater than 1.0 are indicative of biomagnification and typically apply to organic chemicals with log K_{ow} values between 4.0 and 9.0. For a given chemical, FCMs tend to be greater at higher trophic levels, although FCMs for trophic level three can be higher than those for trophic level four.

Food chain multipliers used to derive baseline BAF_ℓ^{fd}s using Procedure #1 can be selected from model-derived or field-derived estimates.

a. **Model-Derived FCMs.** For nonionic organic chemicals appropriate for Procedure #1, EPA has calculated FCMs for various K_{ow} values and trophic levels using the bioaccumulation model of Gobas (1993). The FCMs shown in Table 5-1 were calculated using the Gobas model as the ratio of the baseline BAF_ℓ^{fd}s for trophic levels 2, 3, and 4 to the baseline BCF_ℓ^{fd}.

EPA recommends using the biomagnification model by Gobas (1993) to derive FCMs for nonionic organic chemicals for several reasons. First, the Gobas model includes both benthic and pelagic food chains, thereby incorporating exposure of organisms to chemicals from both the sediment and the water column. Second, the input data needed to run the model can be readily defined. Third, the predicted BAFs using the model are in agreement with field-measured BAFs for chemicals, even those with very high log K_{ow}s. Finally, the model predicts chemical residues in benthic organisms using equilibrium partitioning theory, which is consistent with EPA's equilibrium partitioning sediment guidelines (USEPA, 2000d).

The Gobas model requires input of specific data on the structure of the food chain and the water quality characteristics of the water body of interest. For calculating national BAFs, a mixed pelagic/benthic food web structure consisting of four trophic levels is assumed. Trophic level 1 is phytoplankton, trophic level 2 is

zooplankton, trophic level 3 is forage fish (e.g., sculpin and smelt), and trophic level 4 are predatory fish (e.g., salmonids). Additional assumptions are made regarding the composition of the aquatic species' diets (e.g., salmonids consume 10 percent sculpin, 50 percent alewives, and 40 percent smelt), the physical parameters of the aquatic species (e.g., lipid values), and the water quality characteristics (e.g., water temperature, sediment organic carbon).

A mixed pelagic/benthic food web structure has been assumed for the purpose of calculating FCMs because it is considered to be most representative of the types of food webs that occur in aquatic ecosystems. FCMs derived using the mixed pelagic/benthic structure are also about mid-range in magnitude between a 100% pelagic and 100% benthic driven food web (see the Bioaccumulation TSD). The validity of FCMs derived using the mixed pelagic/benthic food web structure has

Table 5-1
Food-Chain Multipliers for Trophic Levels 2, 3 and 4
(Mixed Pelagic and Benthic Food Web Structure and $\prod_{socw} / K_{OW} = 23$)

Log K_{OW}	Trophic Level 2	Trophic Level 3	Trophic Level 4	Log K_{OW}	Trophic Level 2	Trophic Level 3	Trophic Level 4
4.0	1.00	1.23	1.07	6.6	1.00	12.9	23.8
4.1	1.00	1.29	1.09	6.7	1.00	13.2	24.4
4.2	1.00	1.36	1.13	6.8	1.00	13.3	24.7
4.3	1.00	1.45	1.17	6.9	1.00	13.3	24.7
4.4	1.00	1.56	1.23	7.0	1.00	13.2	24.3
4.5	1.00	1.70	1.32	7.1	1.00	13.1	23.6
4.6	1.00	1.87	1.44	7.2	1.00	12.8	22.5
4.7	1.00	2.08	1.60	7.3	1.00	12.5	21.2
4.8	1.00	2.33	1.82	7.4	1.00	12.0	19.5
4.9	1.00	2.64	2.12	7.5	1.00	11.5	17.6
5.0	1.00	3.00	2.51	7.6	1.00	10.8	15.5
5.1	1.00	3.43	3.02	7.7	1.00	10.1	13.3
5.2	1.00	3.93	3.68	7.8	1.00	9.31	11.2
5.3	1.00	4.50	4.49	7.9	1.00	8.46	9.11
5.4	1.00	5.14	5.48	8.0	1.00	7.60	7.23
5.5	1.00	5.85	6.65	8.1	1.00	6.73	5.58
5.6	1.00	6.60	8.01	8.2	1.00	5.88	4.19
5.7	1.00	7.40	9.54	8.3	1.00	5.07	3.07
5.8	1.00	8.21	11.2	8.4	1.00	4.33	2.20
5.9	1.00	9.01	13.0	8.5	1.00	3.65	1.54
6.0	1.00	9.79	14.9	8.6	1.00	3.05	1.06
6.1	1.00	10.5	16.7	8.7	1.00	2.52	0.721
6.2	1.00	11.2	18.5	8.8	1.00	2.08	0.483
6.3	1.00	11.7	20.1	8.9	1.00	1.70	0.320
6.4	1.00	12.2	21.6	9.0	1.00	1.38	0.210
6.5	1.00	12.6	22.8				

been evaluated in several different ecosystems including Lake Ontario, the tidally influenced Bayou D'Inde in Louisiana, the Fox River and Green Bay, Wisconsin, and the Hudson River in New York. Additional details of the validation of EPA's national default FCMs and the assumptions, uncertainties, and input parameters for the model are provided in the Bioaccumulation TSD.

Although EPA uses the FCMs in Table 5-1 to derive its national 304(a) criteria, EPA recognizes that food webs of other waterbodies might differ from the assumptions used to calculate national BAFs. In these situations, States and authorized Tribes may wish to use alternate food web structures for calculating FCMs for use in setting State or Tribal water quality criteria. Additional guidance on the use of alternate food web structures for calculating State, Tribal, or site-specific criteria is provided in the Bioaccumulation TSD.

b. **Field-Derived FCMs.** In addition to model-derived estimates of FCMs, field data may also be used to derive FCMs. Currently, the use of field-derived FCMs is the only method recommended for estimating FCMs for inorganic and organometalic chemicals because appropriate model-derived estimates are not yet available (see Section 5.6). In contrast to the model-based FCMs described previously, field-derived FCMs account for any metabolism of the chemical of concern by the aquatic organisms used to calculate the FCM.

Field-derived FCMs should be calculated using lipid-normalized concentrations of the nonionic organic chemical in appropriate predator and prey species using the following equations.

$$FCM_{TL2} = BMF_{TL2} \quad \text{(Equation 5-21)}$$

$$FCM_{TL3} = (BMF_{TL3})\,(BMF_{TL2}) \quad \text{(Equation 5-22)}$$

$$FCM_{TL4} = (BMF_{TL4})\,(BMF_{TL3})\,(BMF_{TL2}) \quad \text{(Equation 5-23)}$$

where:

FCM = Food chain multiplier for designated trophic level (TL2, TL3, or TL4)
BMF = Biomagnification factor for designated trophic level (TL2, TL3, or TL4)

The basic difference between FCMs and BMFs is that FCMs relate back to trophic level one (or trophic level two as assumed by the Gobas (1993) model), whereas BMFs always relate back to the next lowest trophic level. For nonionic organic chemicals, BMFs can be calculated from tissue residue concentrations determined in biota at a site according to the following equations.

$$BMF_{TL2} = (C_{\ell, TL2}) / (C_{\ell, TL1}) \quad \text{(Equation 5-24)}$$

$$BMF_{TL3} = (C_{\ell, TL3}) / (C_{\ell, TL2}) \quad \text{(Equation 5-25)}$$

$$BMF_{TL4} = (C_{\ell, TL4}) / (C_{\ell, TL3}) \quad \text{(Equation 5-26)}$$

where:

C_ℓ = Lipid-normalized concentration of chemical in tissue of appropriate biota that occupy the specified trophic level (TL2, TL3, or TL4)

In addition to the acceptability guidelines pertaining to field-measured BAFs, the following procedural and quality assurance requirements apply to field-measured FCMs.

(1) Information should be available to identify the appropriate trophic levels for the aquatic organisms and appropriate predator-prey relationships for the site from which FCMs are being determined. General information on determining trophic levels of aquatic organisms can be found in USEPA 2000a,b,c.

(2) The aquatic organisms sampled from each trophic level should reflect the most important exposure pathways leading to human exposure via consumption of aquatic organisms. For higher trophic levels (e.g., 3 and 4), aquatic species should also reflect those that are commonly consumed by humans.

(3) The studies from which the FCMs are derived should contain sufficient supporting information from which to determine that tissue samples were collected and analyzed using appropriate, sensitive, accurate, and precise methods.

(4) The percent lipid should be either measured or reliably estimated for the tissue used to determine the FCM.

(5) The tissue concentrations should reflect average exposure over the approximate time required to achieve steady-state in the target species.

D. Baseline BAF_ℓ^{fd} from a K_{ow} and FCM

The fourth method in Procedure #1 consists of using a K_{ow} and an appropriate FCM for estimating the baseline BAF_ℓ^{fd}. In this method, the K_{ow} is assumed to be equal to the baseline BCF_ℓ^{fd}. Numerous investigations have demonstrated a linear relationship between the logarithm of the BCF and the logarithm of the octanol-water partition coefficient (K_{ow}) for organic chemicals for fish and other aquatic organisms. Isnard and Lambert (1988) list various regression equations that illustrate this linear relationship. When the regression equations are constructed using lipid-normalized BCFs, the slopes and intercepts are not significantly different from one and zero, respectively (e.g., de Wolf, et al., 1992). The underlying assumption for the linear relationship between the BCF and K_{ow} is that the bioconcentration process can be viewed as the partitioning of a chemical between the lipid of the aquatic organisms and water and that the K_{ow} is a useful surrogate for this partitioning process (Mackay, 1982). To account for biomagnification, Procedure #1 requires the K_{ow} value be used in conjunction with an appropriate FCM.

1. **Baseline BAF_{ℓ}^{fd} Equation.** For each acceptable K_{ow} value and FCM for the chemical of concern, calculate a baseline BAF_{ℓ}^{fd} using the following equation.

$$\text{Baseline } BAF_{\ell}^{fd} = (FCM) \cdot (K_{ow}) \qquad \text{(Equation 5-27)}$$

where:

Baseline BAF_{ℓ}^{fd}	=	BAF expressed on a freely dissolved and lipid-normalized basis for a given trophic level
FCM	=	The food chain multiplier for the appropriate trophic level obtained from Table 5-1 by linear interpolation or from appropriate field data (used with Procedure #1 only)
K_{ow}	=	Octanol-water partition coefficient

The BCF-K_{ow} relationship has been developed primarily for nonionic organic chemicals that are not readily metabolized by aquatic organisms and thus is most appropriate for poorly-metabolized nonionic organic chemicals (i.e., Procedures #1 and #3 as depicted in Figure 5-1). For poorly-metabolized nonionic organic chemicals with large log K_{ow}s (i.e., > 6), reported log BCFs are often not equal to log K_{ow}. EPA believes that this nonlinearity is primarily due to not accounting for several factors which affect the BCF determination. These factors include not basing BCFs on the freely dissolved concentration in water, not accounting for growth dilution, not assessing BCFs at steady-state, inaccuracies in measurements of uptake and elimination rate constants, and complications from the use of solvent carriers in the exposure. Application of Equation 5-27 for predicting BAFs has been conducted in several different ecosystems including Lake Ontario, the tidally influenced Bayou D'Inde in Louisiana, the Fox River and Green Bay, Wisconsin, and the Hudson River in New York. Additional detail on the validation, technical basis, assumptions, and uncertainty associated with Equation 5-27 and is provided in the Bioaccumulation TSD.

2. **FCMs and K_{ow}s**. Food chain multipliers and K_{ow} values should be selected as described previously in Procedure #1.

5.4.3.2 Selecting Final Baseline BAF_{ℓ}^{fd}s

After calculating individual baseline BAF_{ℓ}^{fd}s using as many of the methods in Procedure #1 as possible, the next step is to determine a final baseline BAF_{ℓ}^{fd} for each trophic level from the individual baseline BAF_{ℓ}^{fd}s (see Figures 5-1 and 5-2). The final baseline BAF_{ℓ}^{fd} will be used in the last step to determine the national BAF for each trophic level. The final baseline BAF_{ℓ}^{fd} for each trophic level should be determined from the individual baseline BAF_{ℓ}^{fd}s by considering the data preference hierarchy defined by Procedure #1 and uncertainty in the data. The data preference hierarchy for Procedure #1 is (in order of preference):

1. a baseline BAF_{ℓ}^{fd} from an acceptable field-measured BAF (method 1)

2. a baseline BAF_{ℓ}^{fd} predicted from an acceptable field-measured BSAF (method 2),
3. a baseline BAF_{ℓ}^{fd} predicted from an acceptable BCF and FCM (method 3), or
4. a baseline BAF_{ℓ}^{fd} predicted from an acceptable K_{ow} and FCM (method 4).

This data preference hierarchy reflects EPA's preference for BAFs based on field-measurements of bioaccumulation (methods 1 and 2) over those based on laboratory-measurements and/or predictions of bioaccumulation (methods 3 and 4). However, this data preference hierarchy should not be considered inflexible. Rather, it should be used as a guide for selecting the final baseline BAF_{ℓ}^{fd}s when the uncertainty is similar among two or more baseline BAF_{ℓ}^{fd}s derived using different methods. The following steps and guidelines should be followed for selecting the final baseline BAF_{ℓ}^{fd}s using Procedure #1.

1. **Calculate Species-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method where more than one acceptable baseline BAF_{ℓ}^{fd} is available for a given species, calculate a species-mean baseline BAF_{ℓ}^{fd} as the geometric mean of all available individual baseline BAF_{ℓ}^{fd}s. When calculating a species-mean baseline BAF_{ℓ}^{fd}, individual baseline BAF_{ℓ}^{fd}s should be reviewed carefully to assess the uncertainty in the BAF values. For highly hydrophobic chemicals applicable to Procedure #1, particular attention should be paid to whether sufficient spatial and temporal averaging of water and tissue concentrations was likely achieved in the BAF, BSAF, or BCF study. Highly uncertain baseline BAF_{ℓ}^{fd}s should not be used. Large differences in individual baseline BAF_{ℓ}^{fd}s for a given species (e.g., greater than a factor of 10) should be investigated further. In such cases, some or all of the baseline BAF_{ℓ}^{fd}s for a given species might not be used. Additional discussion on evaluating acceptability of BAF values is provided in the Bioaccumulation TSD.

2. **Calculate Trophic-Level-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method where more than one acceptable species-mean baseline BAF_{ℓ}^{fd} is available within a given trophic level, calculate a trophic-level-mean baseline BAF_{ℓ}^{fd} as the geometric mean of acceptable species-mean baseline BAF_{ℓ}^{fd}s in that trophic level. Trophic-level-mean baseline BAF_{ℓ}^{fd}s should be calculated for trophic levels two, three, and four because available data on U.S. consumers of fish and shellfish indicate significant consumption of organisms in these trophic levels.

3. **Select a Final Baseline BAF_{ℓ}^{fd} for Each Trophic Level.** For each trophic level, select the final baseline BAF_{ℓ}^{fd} using best professional judgment by considering: (1) the data preference hierarchy shown previously, (2) the relative uncertainty in the trophic-level-mean baseline BAF_{ℓ}^{fd}s derived using different methods, and (3) the weight of evidence among the four methods.

    a. In general, when more than one trophic-level-mean baseline BAF_{ℓ}^{fd} is available for a given trophic level, the final trophic-level-mean baseline BAF_{ℓ}^{fd} should be selected from the most preferred BAF method defined by the data preference hierarchy for Procedure #1.

    b. If uncertainty in a trophic-level-mean baseline BAF based on a higher tier (more preferred) method is judged to be substantially greater than a trophic-level-mean

baseline BAF from a lower tier method, and the weight of evidence among the various methods suggests that a BAF value from lower tier method is likely to be more accurate, then the final baseline BAF_{ℓ}^{fd} should be selected using a trophic level-mean baseline BAF_{ℓ}^{fd} from a lower tier method.

c. When considering the weight of evidence among the various BAF methods, greater confidence in the final baseline BAF_{ℓ}^{fd} is generally assigned when BAFs from a greater number of methods are in agreement for a given trophic level. However, lack of agreement among methods does not necessarily indicate less confidence if such disagreements can be adequately explained. For example, if the chemical of concern is metabolized by aquatic organisms represented by a BAF value, one would expect disagreement between a field-measured BAF (the highest priority data) and a predicted BAF using a K_{ow} and model-derived FCM. Thus, field-measured BAFs should generally be given the greatest weight among methods because they reflect direct measures of bioaccumulation and incorporate any metabolism which might occur in the organism and its food web.

d. The above steps should be performed for each trophic level until a final baseline BAF_{ℓ}^{fd} is selected for trophic levels two, three, and four.

5.4.3.3 Calculating National BAFs

The last step in deriving a national BAF for each trophic level is to convert the final baseline BAF_{ℓ}^{fd} determined in the previous step to a BAF that reflects conditions to which the national 304(a) criteria will apply (Figure 5-2). Since a baseline BAF_{ℓ}^{fd} is by definition normalized by lipid content and expressed on a freely dissolved basis, it needs to be adjusted to reflect the lipid fraction of aquatic organisms commonly consumed in the U.S. and the freely dissolved fraction expected in U.S. bodies of water. Converting a final baseline BAF_{ℓ}^{fd} to a national BAF requires information on: (1) the percent lipid of the aquatic organisms commonly consumed by humans, and (2) the freely dissolved fraction of the chemical of concern that would be expected in the ambient waters of interest. For each trophic level, a national BAF should be determined from a final baseline BAF_{ℓ}^{fd} according to the following guidelines.

1. **National BAF Equation.** For each trophic level, calculate a national BAF using the following equation.

$$\text{National BAF}_{(TL\ n)} = [(\text{Final Baseline BAF}_{\ell}^{fd})_{TL\ n} \cdot (f_{\ell})_{TL\ n} + 1] \cdot (f_{fd}) \qquad \text{(Equation 5-28)}$$

where:

Final Baseline BAF_{ℓ}^{fd} = Final trophic-level-mean baseline BAF expressed on a freely dissolved and lipid-normalized basis for trophic level "n"

$f_{\ell(TL\ n)}$	=	Lipid fraction of aquatic species consumed at trophic level "n"
f_{fd}	=	Fraction of the total chemical in water that is freely dissolved

The technical basis of Equation 5-28 is provided in the Bioaccumulation TSD. Guidance for determining each component of Equation 5-28 is provided below.

2. **Determining the Final Baseline BAF_{ℓ}^{fd}.** The final trophic-level-mean baseline BAF_{ℓ}^{fd}s used in this equation are those which have been determined using the guidance presented in Section 5.4.3.2 for selecting the final baseline BAF_{ℓ}^{fd}s.

3. **Lipid Content of Commonly Consumed Aquatic Species.** As illustrated by Equation 5-28, the percent lipid of the aquatic species consumed by humans is needed to accurately characterize the potential exposure to a chemical from ingestion of aquatic organisms.

   a. **National Default Lipid Values.** For the purposes of calculating a national 304(a) criterion, the following national default values for lipid fraction should be used: 1.9% (for trophic level two organisms), 2.6% (for trophic level three organisms), and 3.0% (for trophic level four organisms).

      These national default values for lipid content reflect national per capita average patterns of fish consumption in the United States. Specifically, they were calculated using the consumption-weighted mean lipid content of commonly consumed fish and shellfish as identified by the USDA Continuing Survey of Food Intake by Individuals (CSFII) for 1994 through 1996. This same national survey data was used to derive national default values of fish consumption. To maintain consistency with the fish consumption assumptions, only freshwater and estuarine organisms were included in the derivation of the national default lipid values. Additional details on the technical basis, assumptions, and uncertainty in the national default values of lipid fraction are provided in the Bioaccumulation TSD.

      Although national default lipid values are used by EPA to set national 304(a) criteria, EPA encourages States and authorized Tribes to use local or regional data on lipid content of consumed aquatic species when adopting criteria into their water quality standards because local or regional consumption patterns (and lipid content) can differ from national consumption patterns. Additional guidance on developing site-specific values of lipid content, including a database of lipid content for many commonly consumed aquatic organisms, is found in the Bioaccumulation TSD.

4. **Freely Dissolved Fraction.** The third piece of information required for deriving a national BAF is the freely dissolved fraction of the chemical of concern that is expected

in waters of the United States. As noted previously, expressing BAFs on the freely dissolved concentration in water allows a common basis for averaging BAFs from several studies. However, for use in criteria development, these BAFs should be converted back to values based on the total concentration in the water to be consistent with monitored water column and effluent concentrations, which are typically based on total concentrations of chemicals in the water. This should be done by multiplying the freely dissolved baseline BAF_{ℓ}^{fd} by the fraction of the freely dissolved chemical expected in water bodies of the United States where criteria are to be applied, as shown in Equation 5-29.

$$f_{fd} = \frac{1}{[1 + (POC \cdot K_{ow}) + (DOC \cdot 0.08 \cdot K_{ow})]} \qquad \text{(Equation 5-29)}$$

where:

POC	=	national default value for the particulate organic carbon concentration (kg/L)
DOC	=	national default value for the dissolved organic carbon concentration (kg/L)
K_{ow}	=	n-octanol water partition coefficient for the chemical

Equation 5-29 is identical to Equation 5-12, which was used to determine the freely dissolved fraction for deriving baseline BAF_{ℓ}^{fd}s from field-measured BAFs. However, the POC and DOC concentrations used in Equation 5-29 reflect those values that are expected in U.S. bodies of water, not the POC and DOC values in the study water used to derive the BAF. Guidance for determining each component of Equation 5-29 follows.

a. **National Default Values of POC and DOC.** For estimating the freely dissolved fraction of the chemical of concern that is expected in U.S. water bodies, national default values of 0.5 mg/L (5×10^{-7} kg/L) for POC and 2.9 mg/L (2.9×10^{-6} kg/L) for DOC should be used. These values are 50th percentile values (medians) based on an analysis of over 110,000 DOC values and 85,000 POC values contained in EPA's STORET database from 1980 through 1999. These default values reflect a combination of values for streams, lakes and estuaries across the United States. Additional details on the technical basis, assumptions, and uncertainty in the derivation and application of the national default values of POC and DOC are provided in the Bioaccumulation TSD.

   Although national default values of POC and DOC concentrations are used by EPA to set national 304(a) criteria as described by this document, EPA encourages States and authorized Tribes to use local or regional data on POC and DOC when adopting criteria into their water quality standards. EPA encourages States and Tribes to consider local or regional data on POC and DOC because local or regional conditions may result in differences in POC or DOC

concentrations compared with the values used as national defaults. Additional guidance on developing local or regional values of POC and DOC, including a database of POC and DOC values segregated by waterbody type, is found in the Bioaccumulation TSD.

b. **K_{ow} Value.** The value selected for the K_{ow} of the chemical of concern should be the same value used in earlier calculations (e.g., for calculating baseline BAF_{ℓ}^{fd}s and FCMs). Guidance for selecting the K_{ow} value is found in the Bioaccumulation TSD.

5.4.4 Deriving National BAFs Using Procedure #2

This section provides guidance for calculating national BAFs for nonionic organic chemicals using Procedure #2 shown in Figure 5-1. The types of nonionic organic chemicals for which Procedure #2 is most appropriate are those that are classified as moderately to highly hydrophobic and subject to high rates of metabolism by aquatic biota (see Section 5.4.2 above). Non-aqueous contaminant exposure and subsequent biomagnification in aquatic food webs are not generally of concern for chemicals that are classified in this category. As a result, FCMs are not used in this procedure. In addition, K_{ow} -based predictions of bioconcentration are not used in this procedure since the K_{ow} /BCF relationship is primarily based on poorly metabolized chemicals. Some nonionic organic chemicals for which Procedure #2 is probably appropriate include certain PAHs which are believed to be metabolized substantially by fish (e.g., benzo[a]pyrene, phenanthrene, fluoranthene, pyrene, benzo[a]anthracene and chrysene/triphenylene; USEPA, 1980; Burkhard and Lukasewycz, 2000).

According to Procedure #2, the following three methods can be used in deriving a national BAF:

- using a BAF from an acceptable field study (i.e., a field-measured BAF) (method 1),
- predicting a BAF from an acceptable BSAF (method 2), and
- predicting a BAF from an acceptable BCF (method 3).

Each of these three methods relies on measured data for assessing bioaccumulation and therefore, includes the effects of chemical metabolism by the study organism in the BAF estimate. The field-measured BAF and BSAF methods also incorporate any metabolism which occurs in the aquatic food web.

As shown in Figure 5-2, the next steps in deriving a national BAF after selecting the derivation procedure are: (1) calculating individual baseline BAF_{ℓ}^{fd}s, (2) selecting the final baseline BAF_{ℓ}^{fd}s, and (3) calculating the national BAFs. Each of these three steps is discussed separately below.

5.4.4.1 Calculating Individual Baseline BAF_{ℓ}^{fd}s

As described previously in Procedure #1, calculating individual baseline BAF_{ℓ}^{fd}s involves normalizing the measured BAF_T^t or BCF_T^t (which are based on the total chemical in water and

tissue) by the lipid content of the study organisms and the freely dissolved fraction of the chemical in the study water. Converting measured BAF_T^t (or BCF_T^t) values to baseline BAF_ℓ^{fd} (or BCF_ℓ^{fd}) values is designed to account for variation in measured BAF_T^ts that is caused by differences in lipid content of study organisms and differences in the freely dissolved fraction of chemical in study waters. Therefore, baseline BAF_ℓ^{fd}s are considered more amenable for extrapolating and averaging BAFs across different species and different study waters compared with total BAF_T^ts.

1. For each species where acceptable data are available, calculate all possible baseline BAF_ℓ^{fd}s using each of the three methods shown above for Procedure #2.

2. Individual baseline BAF_ℓ^{fd}s should be calculated from field-measured BAF_T^ts, field-measured BSAFs, and laboratory BCF_T^ts according to the following procedures.

A. Baseline BAF_ℓ^{fd} from Field-Measured BAFs

1. Except where noted below, a baseline BAF_ℓ^{fd} should be calculated from a field-measured BAF_T^t using the guidance and equations outlined in Section 5.4.3.1(A) for determining baseline BAF_ℓ^{fd}s from field-measured BAFs in Procedure #1.

2. Because nonionic organic chemicals applicable to Procedure #2 have relatively high rates of metabolism in aquatic organisms, they will tend to reach steady state more quickly than nonionic organic chemicals with similar K_{ow} values but which undergo little or no metabolism. Therefore, less temporal averaging of chemical concentrations would generally be required for determining field-measured BAF_T^ts with highly metabolizable chemicals compared with chemicals that are poorly metabolized by aquatic biota.

B. Baseline BAF_{ℓ}^{fd} Derived from Field-measured BSAFs

1. A baseline BAF_{ℓ}^{fd} should be calculated from a field-measured BSAF using the guidance and equations outlined in Section 5.4.3.1(B) for determining baseline BAF_{ℓ}^{fd}s from field-measured BSAFs in Procedure #1.

C. Baseline BAF_{ℓ}^{fd} from a Laboratory-Measured BCF

1. Except where noted below, a baseline BAF_{ℓ}^{fd} should be calculated from a laboratory-measured BCF_T^t using the guidance and equations outlined in Section 5.4.3.1(c) for determining baseline BAF_{ℓ}^{fd}s from a laboratory-measured BCF and FCM in Procedure #1.

2. Because biomagnification is not an overriding concern for nonionic organic chemicals applicable to Procedure #2, food chain multipliers are not used in the derivation of a baseline BAF_{ℓ}^{fd} from a laboratory-measured BCF_T^t .

5.4.4.2 Selecting Final Baseline BAF_{ℓ}^{fd}s

After calculating individual, baseline BAF_{ℓ}^{fd}s using as many of the methods in Procedure #2 as possible, the next step is to determine a final baseline BAF_{ℓ}^{fd} for each trophic level from the individual baseline BAF_{ℓ}^{fd}s. The final baseline BAF_{ℓ}^{fd} will be used in the last step to determine the national BAF for each trophic level. A final baseline BAF_{ℓ}^{fd} for each trophic level should be determined from the individual baseline BAF_{ℓ}^{fd}s by considering the data preference hierarchy defined by Procedure #2 and uncertainty in the data. The data preference hierarchy for Procedure #2 is (in order of preference):

1. a baseline BAF_{ℓ}^{fd} from an acceptable field-measured BAF (method 1),
2. a baseline BAF_{ℓ}^{fd} from an acceptable field-measured BSAF (method 2), or
3. a baseline BAF_{ℓ}^{fd} from an acceptable laboratory-measured BCF (method 3).

This data preference hierarchy reflects EPA's preference for BAFs based on field-measurements of bioaccumulation (methods 1 and 2) over those based on laboratory-measurements (method 3). However, as explained in Procedure #1, this data preference hierarchy should not be considered inflexible. Rather, it should be used as a guide for selecting the final baseline BAF_{ℓ}^{fd}s when the underlying uncertainty is similar among two or more baseline BAF_{ℓ}^{fd}s derived using different methods. Although biomagnification is not generally a concern for chemicals subject to Procedure #2, trophic level differences in bioaccumulation might be substantial to the extent that the rate of chemical metabolism by organisms in different trophic levels differs. For example, certain PAHs have been shown to be metabolized to a much greater extent by some fish compared with some invertebrate species (James, 1989). Therefore, final baseline BAF_{ℓ}^{fd}s for chemicals applicable to Procedure #2 should be determined on a trophic-level-specific basis according to the following guidelines.

1. The final baseline BAF_{ℓ}^{fd}s in Procedure #2 should be selected according to the same steps described in Procedure #1 but with the substitution of the data preference hierarchy described above for Procedure #2. Specifically, the species-mean baseline BAF_{ℓ}^{fd}s,

trophic-level-mean baseline BAF_{ℓ}^{fd}s, and the final baseline BAF_{ℓ}^{fd}s should be determined according to the guidelines presented in Procedure #1 (Section 5.4.3.2, Steps 1, 2, and 3).

5.4.4.3 Calculating the National BAFs

As described in Procedure #1, the last step in deriving national BAFs for nonionic organic chemicals is to convert the final baseline BAF_{ℓ}^{fd}s determined in the previous step to BAFs which reflect conditions to which the national 304(a) criteria will apply (Figure 5-2).

1. For trophic levels two, three, and four, national BAFs should be calculated from the final baseline BAF_{ℓ}^{fd}s using the same equation and procedures described previously in Procedure #1 (see Section 5.4.3.3 entitled "Calculating the National BAFs").

5.4.5 Deriving National BAFs Using Procedure #3

This section provides guidance for calculating national BAFs for nonionic organic chemicals using Procedure #3 shown in Figure 5-1. The types of nonionic organic chemicals for which Procedure #3 is most appropriate are those that are classified as low in hydrophobicity (i.e., log K_{ow} values less than 4.0) and subject to low (or unknown) rates of metabolism by aquatic biota (see Section 5.4.2 above). Non-aqueous contaminant exposure and subsequent biomagnification in aquatic food webs are not generally of concern for chemicals that are classified in this category (Fisk et al., 1998; Gobas et al., 1993; Connolly and Pedersen, 1988; Thomann, 1989). As a result, FCMs are not used in this procedure.

According to Procedure #3, the following three methods can be used in deriving a national BAF:

- using a BAF from an acceptable field study (i.e., a field-measured BAF),
- predicting a BAF from an acceptable laboratory-measured BCF, and
- predicting a BAF from an acceptable K_{ow}.

After selecting the derivation procedure, the next steps in deriving a national BAF at a given trophic level for nonionic organic chemicals are: (1) calculating individual baseline BAF_{ℓ}^{fd}s, (2) selecting the final baseline BAF_{ℓ}^{fd}, and (3) calculating the national BAF (Figure 5-2). Each of these three steps is discussed separately below.

5.4.5.1 Calculating Individual Baseline BAF_{ℓ}^{fd}s

Calculating individual baseline BAF_{ℓ}^{fd}s involves normalizing each measured BAF_{T}^{t} or BCF_{T}^{t} (which are based on the total chemical in water and tissue) by the lipid content of the study organism and the freely dissolved fraction of the chemical in the study water. For additional discussion of the technical basis for calculating baseline BAF_{ℓ}^{fd}s, see Section 5.4.3.1 in Procedure #1.

1. For each species where acceptable data are available, calculate all possible baseline BAF_{ℓ}^{fd}s using each of the three methods shown above for Procedure #3.

2. An individual baseline BAF_{ℓ}^{fd} should be calculated from field-measured BAF_{T}^{t}s, laboratory-measured BCF_{T}^{t}s, and K_{ow} values according to the following procedures.

A. Baseline BAF_{ℓ}^{fd} from Field-Measured BAFs

1. Except where noted below, a baseline BAF_{ℓ}^{fd} should be calculated from a field-measured BAF_{T}^{t} using the guidance and equations outlined in Section 5.4.3.1(A) in Procedure #1.

2. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), nonionic organic chemicals applicable to Procedure #3 are expected to remain almost entirely in the freely dissolved form in natural waters with dissolved and particulate organic carbon concentrations typical of most field BAF studies. Therefore, the freely dissolved fraction should be assumed to be equal to 1.0, unless the concentrations of DOC and POC are very high in the field BAF study. For studies with very high DOC or POC concentrations, (e.g., about 100 mg/L or higher for DOC or 10 mg/L or higher for POC), the freely dissolved fraction may be substantially lower than 1.0 and therefore should be calculated using Equation 5-12.

3. **Temporal Averaging of Concentrations.** Also due to their low hydrophobicity, nonionic organic chemicals appropriate to Procedure #3 will also tend to reach steady state quickly compared with those chemicals to which Procedure #1 applies. Therefore, the extent of temporal averaging of tissue and water concentrations is typically much less than that required for highly hydrophobic chemicals to which Procedure #1 is applied. In addition, field studies used to calculate BAFs for these chemicals should have sampled water and tissue at similar points in time because tissue concentrations respond more rapidly to changes in water concentrations. EPA will be providing additional guidance on appropriate BAF study designs for nonionic organic chemicals (including those appropriate to Procedure #3) in its forthcoming guidance document on conducting field BAF and BSAF studies.

B. Baseline BAF_{ℓ}^{fd} from a Laboratory-Measured BCF

1. Except where noted below, a baseline BAF_{ℓ}^{fd} should be calculated from a laboratory-measured BCF_{T}^{t} using the guidance and equations outlined in Section 5.4.3.1(c) of Procedure #1.

2. **Food Chain Multipliers.** Because biomagnification is not an overriding concern for the minimally hydrophobic chemicals applicable to Procedure #3, FCMs are not used in the derivation of a baseline BAF_{ℓ}^{fd} from a laboratory-measured BCF_{T}^{t}.

3. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), nonionic organic chemicals to which Procedure #3 is applied are expected to remain

almost entirely in the freely dissolved form in waters containing dissolved and particulate organic carbon concentrations typical of laboratory BCF studies. Therefore, the freely dissolved fraction should usually be assumed equal to 1.0. The freely dissolved fraction will be substantially less than 1.0 only in situations where unusually high concentrations of DOC and POC are present in the laboratory BCF study (e.g., above about 100 mg/L for DOC or about 10 mg/L for POC). In this situation, the freely dissolved fraction should be calculated according to Equation 5-12.

C. Baseline BAF_{ℓ}^{fd} from a K_{ow}

1. Except where noted below, a baseline BAF_{ℓ}^{fd} should be calculated from an acceptable K_{ow} using the guidance and equations outlined in Section 5.4.3.1(D) in Procedure #1.

2. Because biomagnification is not an overriding concern for nonionic organic chemicals with low hydrophobicity (i.e., log $K_{ow} < 4.0$), food chain multipliers are not used in Procedure #3 for deriving the baseline BAF_{ℓ}^{fd} from a K_{ow}.

5.4.5.2 Selecting Final Baseline BAF_{ℓ}^{fd}s

After calculating individual baseline BAF_{ℓ}^{fd}s using as many of the methods in Procedure #3 as possible, the next step is to determine a final baseline BAF_{ℓ}^{fd} for each trophic level from the individual baseline BAF_{ℓ}^{fd}s (Figure 5-2). The final baseline BAF_{ℓ}^{fd} will be used in the last step to determine the national BAF for each trophic level. The final baseline BAF_{ℓ}^{fd} for each trophic level should be determined from the individual baseline BAF_{ℓ}^{fd}s by considering the data preference hierarchy defined by Procedure #3 and uncertainty in the data. The data preference hierarchy for Procedure #3 is (in order of preference):

1. a baseline BAF_{ℓ}^{fd} from an acceptable field-measured BAF or laboratory-measured BCF, or
2. a baseline BAF_{ℓ}^{fd} predicted from an acceptable K_{ow} value.

This data preference hierarchy reflects EPA's preference for BAFs that are based on measured data (field-measured BAFs and laboratory-measured BCFs) over BAFs based on predictive methods (K_{ow}). This data preference hierarchy should be used as a guide for selecting the final baseline BAF_{ℓ}^{fd}s when the uncertainty is similar among two or more baseline BAF_{ℓ}^{fd}s derived using different methods. Since bioaccumulation via dietary uptake and subsequent biomagnification generally are not of concern for chemicals subject to Procedure #3, field-measured BAFs and laboratory-measured BCFs are considered equally in determining the national BAF.

Final baseline BAF_{ℓ}^{fd}s should be selected for each trophic level using the following steps and guidelines.

1. **Calculate Species-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method (i.e., field-measured BAF, BAF from a lab-measured BCF, or BAF from a K_{ow}) where more than one

acceptable baseline BAF_{ℓ}^{fd} is available for a given species, calculate a species-mean baseline BAF_{ℓ}^{fd} according to the guidance described previously in Procedure #1.

2. **Calculate Trophic-Level-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method where more than one acceptable species-mean baseline BAF_{ℓ}^{fd} is available within a given trophic level, calculate the trophic-level-mean baseline BAF_{ℓ}^{fd} as the geometric mean of acceptable species-mean baseline BAF_{ℓ}^{fd}s in that trophic level.

3. **Select a Final Baseline BAF_{ℓ}^{fd} for Each Trophic Level.** For each trophic level, select the final baseline BAF_{ℓ}^{fd} using best professional judgment by considering: (1) the data preference hierarchy, (2) the relative uncertainties among trophic-level-mean baseline BAF_{ℓ}^{fd}s derived using different methods, and (3) the weight of evidence among the three methods.

   a. In general, when more than one trophic-level-mean baseline BAF_{ℓ}^{fd} is available within a given trophic level, the final baseline BAF_{ℓ}^{fd} should be selected from the most preferred BAF method defined by the data preference hierarchy for Procedure #3. Within the first data preference tier, field-measured BAFs and laboratory-measured BCFs are considered equally desirable for deriving a final trophic-level-mean baseline BAF_{ℓ}^{fd} using Procedure #3. If a trophic-level-mean baseline BAF_{ℓ}^{fd} is available from both a field-measured BAF and a laboratory-measured BCF, the final baseline BAF_{ℓ}^{fd} should be selected using the trophic-level-mean baseline BAF_{ℓ}^{fd} or BCF_{ℓ}^{fd} with the least overall uncertainty.

   b. If uncertainty in a trophic-level-mean baseline BAF_{ℓ}^{fd} based on a higher tier (more preferred) method is judged to be substantially greater than a trophic-level-mean baseline BAF_{ℓ}^{fd} from a lower tier method, then the final baseline BAF_{ℓ}^{fd} should be selected using a trophic-level-mean baseline BAF_{ℓ}^{fd} from a lower tier method.

   c. The above steps should be performed for each trophic level until a final baseline BAF_{ℓ}^{fd} is selected for trophic level two, three, and four.

5.4.5.3 Calculating the National BAFs

As described in Procedure #1, the last step in deriving a national BAF for a given trophic level for nonionic organic chemicals is to convert the final baseline BAF_{ℓ}^{fd} determined in the previous step to a BAF that reflect conditions to which the national 304(a) criterion will apply (Figure 5-2). Each national BAF should be determined from a final baseline BAF_{ℓ}^{fd} according to the following guidelines.

1. **National BAF Equation.** Except where noted below, national BAFs for trophic levels two, three, and four should be calculated from the final, trophic-level-mean baseline BAF_{ℓ}^{fd}s using Equation 5-28 and associated guidance described in Procedure #1 (see Section 5.4.3.3).

2. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), a freely dissolved fraction of 1.0 should be assumed for calculating national BAFs for nonionic organic chemicals using Procedure #3. A freely dissolved fraction of 1.0 should be assumed because at a log K_{ow} of less than 4.0, nonionic organic chemicals are expected to remain over 99 percent in the freely dissolved form at POC and DOC concentrations corresponding to national default values for U.S. bodies of water (i.e., 0.5 mg/L and 2.9 mg/L, respectively).

5.4.6 Deriving National BAFs Using Procedure #4

This section provides guidance for calculating national BAFs for nonionic organic chemicals using Procedure #4 shown in Figure 5-1. The types of nonionic organic chemicals for which Procedure #4 is most appropriate are those that are classified as having low hydrophobicity and subject to high rates of metabolism by aquatic biota (see Section 5.4.2 above). Non-aqueous contaminant exposure and subsequent biomagnification in aquatic food webs are not generally of concern for chemicals that are classified in this category. As a result, FCMs are not used in this procedure. In addition, K_{ow} -based predictions of bioconcentration are not used in this procedure since the K_{ow} /BCF relationship is primarily based on poorly metabolized chemicals. One example of a nonionic organic chemical for which Procedure #4 appears appropriate is butyl benzyl phthalate in fish. Using radiolabeling techniques with confirmation by chromatographic analysis, Carr et al. (1997) present evidence that indicates butyl benzyl phthalate is extensively metabolized in sunfish. Carr et al. (1997) also report measured BCFs (and subsequently lipid-normalized BCFs) which are substantially below predicted BCFs based on log $K_{ow.}$ In a study of chlorinated anilines (which would be essentially un-ionized at ambient pH), de Wolf et al. (1992) reported measured BCFs substantially lower than those predicted based on K_{ow}. The authors suggested that biotransformation (metabolism) involving the amine (NH_2) was responsible for the lower measured BCFs.

According to Procedure #4, the following two methods can be used in deriving a national BAF:

- using a BAF from an acceptable field study (i.e., a field-measured BAF), and
- predicting a BAF from an acceptable BCF.

After selecting the derivation procedure, the next steps in deriving a national BAF for a given trophic level for nonionic organic chemicals are: (1) calculating individual baseline BAF_{ℓ}^{fd}s, (2) selecting the final baseline BAF_{ℓ}^{fd}, and (3) calculating the national BAF (Figure 5-2). Each of these three steps is discussed separately below.

5.4.6.1 Calculating Individual Baseline BAF_{ℓ}^{fd}s

Calculating individual baseline BAF_{ℓ}^{fd}s involves normalizing the measured BAF_T^t or BCF_T^t (which are based on the total chemical in water and tissue) by the lipid content of the study organism and the freely dissolved fraction of the chemical in the study water. For additional discussion of the technical basis for calculating baseline BAF_{ℓ}^{fd}s, see Section 5.4.3.1 in Procedure #1.

1. For each species where acceptable data are available, calculate all possible baseline BAF_{ℓ}^{fd}s using each of the two methods shown above for Procedure #4.

2. Individual baseline BAF_{ℓ}^{fd}s should be calculated from field-measured BAF_{T}^{t}s and laboratory-measured BCF_{T}^{t}s according to the following procedures.

A. Baseline BAF_{ℓ}^{fd} from Field-Measured BAFs

1. A baseline BAF_{ℓ}^{fd} should be calculated from a field-measured BAF_{T}^{t} using the guidance and equations outlined in Section 5.4.3.1(A) in Procedure #1.

2. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), nonionic organic chemicals applicable to Procedure #4 are expected to remain almost entirely in the freely dissolved form in natural waters with dissolved and particulate organic carbon concentrations typical of most field BAF studies. Therefore, the freely dissolved fraction should be assumed equal to 1.0 unless the concentrations of DOC and POC are very high in the field BAF study. For studies with very high DOC or POC concentrations, (e.g., about 100 mg/L or higher for DOC or 10 mg/L or higher for POC), the freely dissolved fraction may be substantially lower than 1.0 and therefore should be calculated using Equation 5-12.

3. **Temporal Averaging of Concentrations.** Also due to their low hydrophobicity, nonionic organic chemicals appropriate to Procedure #4 will also tend to reach steady-state quickly compared with those chemicals to which Procedure #1 applies. Therefore, the extent of temporal averaging of tissue and water concentrations is typically much less than that required for highly hydrophobic chemicals to which Procedure #1 is applied. In addition, field studies used to calculate BAFs for these chemicals should have sampled water and tissue at similar points in time because tissue concentrations should respond rapidly to changes in water concentrations. EPA will be providing additional guidance on appropriate BAF study designs for nonionic organic chemicals (including those appropriate to Procedure #4) in its forthcoming guidance document on conducting field BAF and BSAF studies.

B. Baseline BAF_{ℓ}^{fd} from a Laboratory-Measured BCF

1. Except where noted below, a baseline BAF_{ℓ}^{fd} should be calculated from a laboratory-measured BCF_{T}^{t} using the guidance and equations outlined in Section 5.4.3.1(c) of Procedure #1.

2. **Food Chain Multipliers.** Because biomagnification is not an important concern for the minimally hydrophobic chemicals applicable to Procedure #4, FCMs are not used in the derivation of a baseline BAF_{ℓ}^{fd} from a laboratory-measured BCF_{T}^{t}.

3. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), nonionic organic chemicals to which Procedure #4 is applied are expected to remain

almost entirely in the freely dissolved form in waters containing dissolved and particulate organic carbon concentrations typical of laboratory BCF studies. Therefore, the freely dissolved fraction should usually be assumed to be equal to 1.0. The freely dissolved fraction will be substantially less than 1.0 only in situations where unusually high concentrations of DOC and POC are present in the lab BCF study (e.g., above about 100 mg/L for DOC or about 10 mg/L for POC). In this situation, the freely dissolved fraction should be calculated according to Equation 5-12.

5.4.6.2 Selecting Final Baseline BAF_{ℓ}^{fd}s

After calculating individual baseline BAF_{ℓ}^{fd}s using as many of the methods in Procedure #4 as possible, the next step is to determine a final baseline BAF_{ℓ}^{fd} for a given trophic level from the individual baseline BAF_{ℓ}^{fd}s (Figure 5-2). The final baseline BAF_{ℓ}^{fd} will be used in the last step to determine the national BAF for each trophic level. A final baseline BAF_{ℓ}^{fd} should be determined for each trophic level from the individual baseline BAF_{ℓ}^{fd}s by considering the data preference hierarchy defined by Procedure #4 and uncertainty in the data. The data preference hierarchy for Procedure #4 is:

1. a baseline BAF_{ℓ}^{fd} from an acceptable field-measured BAF or predicted from an acceptable laboratory-measured BCF.

Since bioaccumulation via dietary uptake and subsequent biomagnification generally are not of concern for chemicals subject to Procedure #4, field-measured BAFs and laboratory-measured BCFs are considered equally in determining the national BAF.

Final baseline BAF_{ℓ}^{fd}s should be selected for each trophic level using the following steps and guidelines.

1. **Calculate Species-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method (i.e., field-measured BAF or a BAF from a lab-measured BCF) where more than one acceptable baseline BAF_{ℓ}^{fd} is available for a given species, calculate a species-mean baseline BAF_{ℓ}^{fd} according to the guidance described previously in Procedure #1.

2. **Calculate Trophic-Level-Mean Baseline BAF_{ℓ}^{fd}s.** For each BAF method where more than one acceptable species-mean baseline BAF_{ℓ}^{fd} is available within a given trophic level, calculate the trophic-level-mean baseline BAF_{ℓ}^{fd} as the geometric mean of acceptable species-mean baseline BAF_{ℓ}^{fd}s for that trophic level.

3. **Select a Final Baseline BAF_{ℓ}^{fd} for Each Trophic Level.** For each trophic level, select the final baseline BAF_{ℓ}^{fd} using best professional judgment by considering: (1) the data preference hierarchy, and (2) the relative uncertainties among trophic-level-mean BAFs derived using different methods.

    a. As discussed above, field-measured BAFs and laboratory-measured BCFs are considered equally desirable for deriving a final trophic-level-mean baseline

BAF_{ℓ}^{fd} using Procedure #4. If a trophic-level-mean baseline BAF_{ℓ}^{fd} is available from both a field-measured BAF and a laboratory-measured BCF, the final baseline BAF_{ℓ}^{fd} should be selected using the trophic-level-mean baseline BAF_{ℓ}^{fd} or BCF_{ℓ}^{fd} with the least overall uncertainty.

b. The above steps should be performed for each trophic level until a final baseline BAF_{ℓ}^{fd} is selected for trophic levels two, three, and four.

5.4.6.3 Calculating National BAFs

As described in Procedure #1, the last step in deriving a national BAF for a given trophic level for nonionic organic chemicals is to convert the final baseline BAF_{ℓ}^{fd} determined in the previous step to a BAF that reflects conditions to which the national 304(a) criterion will apply (Figure 5-2). Each national BAF should be determined from a final baseline BAF_{ℓ}^{fd} according to the following guidelines.

1. **National BAF Equation.** Except where noted below, national BAFs for trophic-levels two, three, and four should be calculated from the final, trophic-level-mean baseline BAF_{ℓ}^{fd}s using the same equation and procedures described previously in Procedure #1 (see Section 5.4.3.3 in Procedure #1).

2. **Freely Dissolved Fraction**. Due to their low hydrophobicity (i.e., log K_{ow} < 4.0), a freely dissolved fraction of 1.0 should be assumed for calculating national BAFs for nonionic organic chemicals using Procedure #4. A freely dissolved fraction of 1.0 should be assumed because at a log K_{ow} value of less than 4.0, nonionic organic chemicals are expected to remain over 99 percent in the freely dissolved form at POC and DOC concentrations corresponding to national default values for U.S. bodies of water (i.e., 0.5 mg/L and 2.9 mg/L, respectively).

5.5 NATIONAL BIOACCUMULATION FACTORS FOR IONIC ORGANIC CHEMICALS

This section contains guidelines for deriving national BAFs for ionic organic chemicals (i.e., organic chemicals which undergo significant ionization in water). As defined in Section 5.3.5, ionic organic chemicals contain functional groups which can either readily donate protons (e.g., organic acids with hydroxyl, carboxylic, and sulfonic groups) or readily accept protons (e.g., organic bases with amino and aromatic heterocyclic nitrogen groups). Some examples of ionic organic compounds include:

- chlorinated phenols (e.g., 2,4,6-trichlorophenol, pentachlorophenol),
- chlorinated phenoxyalkanoic acids (e.g., 2,4-dichlorophenoxyacetic acid [2,4-D]),
- nitrophenols (e.g., 2-nitrophenol, 2,4,6-trinitrophenol),
- cresols (e.g., 2,4-dinitro-*o*-cresol [DNOC]),
- pyridines (e.g., 2,4-dimethypyidine),
- aliphatic and aromatic amines (e.g., trimethylamine, aniline), and

- linear alkylbenzenesulfonate (LAS) surfactants.

Ionic organic chemicals are considered separately for deriving national BAFs because the anionic or cationic species of these chemicals behave much differently in the aquatic environment compared with their neutral (un-ionized) counterparts. The neutral species of ionic organic chemicals are thought to behave in a similar manner as nonionic organic compounds (e.g., partitioning to lipids and organic carbon as a function of hydrophobicity). However, the ionized (cationic, anionic) species exhibit a considerably more complex behavior involving multiple environmental partitioning mechanisms (e.g., ion exchange, electrostatic, and hydrophobic interactions) and a dependency on pH and other factors including ionic strength and ionic composition (Jafvert et al., 1990; Jafvert 1990; Schwarzenbach, et al., 1993). As a consequence, methods to predict the environmental partitioning of organic cations and anions are less developed and validated compared with methods for nonionic organic chemicals (Spacie, 1994; Suffet et al., 1994).

Given the current limitations in the state of the science for predicting the partitioning and bioaccumulation of the ionized species of ionic organic chemicals, procedures for deriving national BAFs for these chemicals differ depending on the extent to which the fraction of the total chemical is likely to be represented by the ionized (cationic, anionic) species in U.S. surface waters. When a significant fraction of the total chemical concentration is expected to be present as the ionized species in water, procedures for deriving the national BAF rely on empirical (measured) methods (i.e., Procedures #5 and 6 in Section 5.6). When an insignificant fraction of the total chemical is expected to be present as the ionized species (i.e., the chemical exists essentially in the neutral form), procedures for deriving the national BAF will follow those established for nonionic organic chemicals (e.g., Procedures #1 through #4 in Section 5.4). The following guidelines apply for assessing the occurrence of cationic and anionic forms at typical environmental pH ranges.

1. For the ionic organic chemical of concern, the dissociation constant, pK_a, should be compared to the range of pH values expected in fresh and estuarine waters of the U.S. At pH equal to the pK_a, 50% of the organic acid or base is expected to be present in the ionized species. The pH values for U.S. fresh and estuarine waters typically range between 6 and 9, although somewhat higher and lower values can occur in some bodies of water (e.g., acidic bogs and lakes, highly alkaline and eutrophic systems, etc.).

2. For organic acids, the chemical will exist almost entirely in its un-ionized form when pH is about 2 or more units below the pK_a. For organic bases, the chemical will exist almost entirely in its un-ionized form when pH is about 2 or more units above the pK_a. In these cases, the aqueous behavior of the chemical would be expected to be similar to nonionic organic chemicals. Therefore, national BAF should usually be derived using Procedures #1 through #4 in Section 5.4.

3. When pH is greater than the pK_a minus 2 for organic acids (or less than the pKa plus 2 for organic bases), the fraction of the total chemical that is expected to exist in its ionized form can become significant (i.e., $\geq$1% in the ionized). In these cases, the national BAF should usually be derived using Procedures #5 and #6 in Section 5.6.

4. In general, most organic acids (e.g., pentachlorophenol and silvex), exist primarily in the ionized form in ambient waters because their pK_a's (4.75 and 3.07, respectively) are much smaller than the pH of the ambient waters. Conversely, most organic bases, (e.g., aniline) exist mostly in the un-ionized form in ambient waters because their pK_a's (4.63 for aniline) are much smaller than the pH of the ambient waters.

5. The above guidelines are intended to be a general guide for deriving national BAFs for ionic organic chemicals, not an inflexible rule. Modifications to these guidelines should be considered on a case-by-case basis, particularly when such modifications are strongly supported by measured bioaccumulation or bioconcentration data. For example, initial models have been developed for predicting the solid and organic-phase partitioning of certain organic acids (e.g., Jafvert 1990, Jafvert et al., 1990). As these or other models become more fully developed and appropriately validated in the future, they should be considered in the development of national BAFs. In addition, since pH is a controlling factor for dissociation and subsequent partitioning of ionic organic chemicals, consideration should be given to expressing BAFs or BCFs as a function of pH (or other factors) where sufficient data exist to reliably establish such relationships.

5.6 NATIONAL BIOACCUMULATION FACTORS FOR INORGANIC AND ORGANOMETALLIC CHEMICALS

This section contains guidelines for deriving national BAFs for inorganic and organometallic chemicals as defined in Section 5.3.5. The derivation of BAFs for inorganic and organometallic chemicals differs in several ways from procedures for nonionic organic chemicals. First, lipid normalization of chemical concentrations in tissues does not generally apply for inorganic and organometallic chemicals. Thus, BAFs and BCFs cannot be extrapolated from one tissue to another based on lipid-normalized concentrations as is done for nonionic organic chemicals. Second, the bioavailability of inorganics and organometallics in water tends to be chemical-specific and thus, the techniques for expressing concentrations of nonionic organic chemicals based on the freely dissolved form do not generally apply. Third, at the present time there are no generic bioaccumulation models that can be used to predict BAFs for inorganic and organometallic chemicals as a whole, unlike the existence of K_{ow}-based models for nonionic organic chemicals. While some chemical-specific bioaccumulation models have been developed for inorganic and organometallic chemicals (e.g., Mercury Cycling Model by Hudson et. al, 1994), those models currently tend to require site-specific data for input to the model and are restricted to site-specific applications. As the models become more fully developed and validated in the future, they should be considered on a case-by-case basis in conjunction with the following procedures for deriving national BAFs.

5.6.1 Selecting the BAF Derivation Procedure

As shown in Figure 5-1, national BAFs can be derived using two procedures for inorganic and organometallic chemicals (Procedures #5 and #6). The choice of the BAF derivation procedure depends on whether or not the chemical undergoes biomagnification in aquatic food webs.

1. For many inorganic and organometallic chemicals, biomagnification does not occur and the BCF will be equal to the BAF. For these types of chemicals, Procedure #5 should be used to derive the national BAF. Procedure #5 considers BAFs and BCFs to be of equal value in determining the national BAF and does not require the use of FCMs with BCF measurements. Guidance for deriving BAFs using Procedure #5 is provided in Section 5.6.3.

2. For some inorganic and organometallic chemicals (e.g., methylmercury), biomagnification does occur and Procedure #6 should be used to determine the national BAF. Procedure #6 gives general preference to the use of field-measured BAFs over laboratory-measured BCFs and requires FCMs to be used with BCF measurements for predicting BAFs. Guidance for deriving BAFs using Procedure #6 is provided in Section 5.6.4.

3. Determining whether or not biomagnification occurs for inorganic and organometallic chemicals requires chemical-specific data on measured concentrations of the chemical in aquatic organisms and their prey. Concentrations in aquatic organisms that increase substantially at successive trophic levels of a food web suggest that biomagnification is

occurring. Concentrations in aquatic organisms that remain about the same or decrease at successive trophic levels of a food web suggest that biomagnification is not occurring. When comparing tissue concentrations for assessing biomagnification, care should be taken to ensure that the aquatic organisms chosen actually represent functional predator-prey relationships and that all major prey species are considered in the comparisons.

5.6.2 Bioavailability

The chemical-specific nature of inorganic and organometallic bioavailability is likely due in part to chemical-specific differences in several factors which affect bioavailability and bioaccumulation. These factors include differences in the mechanisms for chemical uptake by aquatic organisms (e.g., passive diffusion, facilitated transport, active transport), differences in sorption affinities to biotic and abiotic ligands, and differences in chemical speciation in water. Some inorganic and organometallic chemicals exist in multiple forms and valence states in aquatic ecosystems that can differ in their bioavailability to aquatic organisms and undergo conversions between forms. For example, selenium can exist in various forms in aquatic ecosystems, including inorganic selenite($^{+4}$) and selenate($^{+6}$) oxyanions, elemental selenium (^{0}) under reducing conditions (primarily in sediments), and organoselenium compounds of selenide ($^{-2}$). Dominant forms of mercury in natural, oxic waters include inorganic ($^{+2}$) mercury compounds and methylmercury; the latter is generally considered to be substantially more bioavailable than inorganic mercury compounds to higher trophic level organisms. Although a generic analogue to the "freely dissolved" conversion for nonionic organic chemicals does not presently exist for inorganic and organometallic chemicals as a whole, the occurrence and bioavailability of different forms of these chemicals should be carefully considered when deriving national BAFs.

1. If data indicate that: (1) a particular form (or multiple forms) of the chemical of concern largely governs its bioavailability to target aquatic organisms, and (2) BAFs are more reliable when derived using the bioavailable form(s) compared with using other form(s) of the chemical of concern, then BAFs and BCFs should be based on the appropriate bioavailable form(s).

2. Because different forms of many inorganic and organometallic chemicals may interconvert once released to the aquatic environment, regulatory and mass balance considerations typically require an accounting of the total concentration in water. In these cases, sufficient data should be available to enable conversion between total concentrations and the other (presumably more bioavailable) forms in water.

5.6.3 Deriving BAFs Using Procedure #5

This section contains guidance for calculating national BAFs for inorganic and organometallic chemicals using Procedure #5 as shown in Figure 5-1. The types of inorganic and organometallic chemicals for which Procedure #5 is appropriate are those that are not likely to biomagnify in aquatic food webs (see Section 5.1 above). In Procedure #5, two methods are available to derive the national BAF for a given trophic level:

- using a BAF from an acceptable field study (i.e., field-measured BAF), or
- predicting a BAF from an acceptable laboratory-measured BCF.

Individual BAFs should be determined from field-measured BAFs or laboratory-measured BCFs according to the following guidelines.

5.6.3.1 Determining Field-Measured BAFs

1. Except where noted below, field-measured BAFs should be determined using the guidance provided in Section 5.4.3.1(A) of Procedure #1.

2. As described previously, conversion of field-measured BAFs to baseline BAF_{ℓ}^{fd}s based on lipid-normalized and freely-dissolved concentrations does not apply for inorganic and organometallic chemicals. Therefore, the guidance and equations provided in Procedure #1 which pertain to converting field-measured BAFs to baseline BAF_{ℓ}^{fd}s and subsequently to national BAFs do not generally apply to inorganic chemicals. As discussed in Section 5.6.2 above, an analogous procedure in concept might be required for converting total BAFs to BAFs based on the most bioavailable form(s) for some inorganic and organometallic chemicals of concern. Such procedures should be applied on a chemical-specific basis.

3. BAFs should be expressed on a wet-weight basis; BAFs reported on a dry-weight basis can be used only if they are converted to a wet-weight basis using a conversion factor that is measured or reliably estimated for the tissue used in the determination of the BAF.

4. BAFs should be based on concentrations in the edible tissue(s) of the biota unless it is demonstrated that whole-body BAFs are similar to edible tissue BAFs. For some finfish and shellfish species, whole body is considered to be the edible tissue.

5. The concentrations of an inorganic or organometallic chemical in a bioaccumulation study should be greater than normal background levels and greater than levels required for normal nutrition of the test species if the chemical is a micronutrient, but below levels that adversely affect the species. Bioaccumulation of an inorganic or organometallic chemical that is essential to the nutrition of aquatic organisms might be overestimated if concentrations are at or below normal background levels due to selective accumulation by the organisms to meet their nutritional requirements.

5.6.3.2 Determining Laboratory-Measured BCFs

1. Except where noted below, BAFs should be predicted from laboratory-measured BCFs using the guidance provided in Section 5.4.3.1(c) of Procedure #1.

2. As described previously, conversion of laboratory-measured BCFs to baseline BCF_{ℓ}^{fd}s based on lipid-normalized and freely dissolved concentrations does not apply for inorganic and organometallic chemicals. Therefore, the guidance and equations provided in Procedure #1 which pertain to converting laboratory-measured BCFs to baseline BCF_{ℓ}^{fd}s and subsequently to national BCFs do not generally apply to inorganic and organometallic chemicals. As discussed in Section 5.6.2 above, an analogous procedure in concept might be required for converting total BCFs to BCFs based on the most bioavailable form(s) of some inorganic and organometallic chemicals of concern. Such procedures should be applied on a chemical-specific basis. In addition, the use of FCMs with BCFs does not apply to chemicals applicable to Procedure #5.

3. BCFs should be expressed on a wet-weight basis; BCFs reported on a dry-weight basis can be used only if they are converted to a wet-weight basis using a conversion factor that is measured or reliably estimated for the tissue used in the determination of the BCF.

4. BCFs should be based on concentrations in the edible tissue(s) of the biota unless it is demonstrated that whole-body BCFs are similar to edible tissue BCFs. For some finfish and shellfish species, whole body is considered to be the edible tissue.

5. The concentrations of an inorganic or organometallic chemical in a bioconcentration test should be greater than normal background levels and greater than levels required for normal nutrition of the test species if the chemical is a micronutrient, but below levels that adversely affect the species. Bioaccumulation of an inorganic or organometallic chemical that is essential to the nutrition of aquatic organisms might be overestimated if concentrations are at or below normal background levels due to selective accumulation by the organisms to meet their nutritional requirements.

5.6.3.3 Determining the National BAFs

After calculating individual BAFs using as many of the methods in Procedure #5 as possible, the next step is to determine national BAFs for each trophic level from the individual BAFs. The national BAFs will be used to determine the national 304(a) criteria. The national BAFs should be determined from the individual BAFs by considering the data preference hierarchy defined for Procedure #5 and uncertainty in the data. The data preference hierarchy for Procedure #5 is:

1. a BAF from an acceptable field-measured BAF or predicted from an acceptable laboratory-measured BCF.

Since bioaccumulation via dietary uptake and subsequent biomagnification are not of concern for chemicals subject to Procedure #5, field-measured BAFs and laboratory-measured

BCFs are considered equally in determining the national BAFs. The national BAFs should be selected for each trophic level using the following steps and guidelines.

1. **Calculate Species-Mean BAFs.** For each BAF method where more than one acceptable field-measured BAF (or a BAF predicted from a BCF) is available for a given species, calculate the species-mean BAF as the geometric mean of all acceptable individual measured or BCF-predicted BAFs. When calculating species-mean BAFs, individual measured or BCF-predicted BAFs should be reviewed carefully to assess uncertainties in the BAF values. Highly uncertain BAFs should not be used. Large differences in individual BAFs for a given species (e.g., greater than a factor of 10) should be investigated further and in such cases, some or all of the BAFs for a given species might not be used. Additional discussion on evaluating the acceptability of BAF and BCF values is provided in the Bioaccumulation TSD.

2. **Calculate Trophic-Level-Mean BAFs.** For each BAF method where more than one acceptable species-mean BAF is available within a given trophic level, calculate the trophic-level-mean BAF as the geometric mean of acceptable species-mean BAFs in that trophic level. Trophic-level-mean BAFs should be calculated for trophic levels two, three and four because available data on U.S. consumers of fish and shellfish indicate significant consumption of organisms in these trophic levels.

3. **Select a Final National BAF for Each Trophic Level.** For each trophic level, select the final national BAF using best professional judgment by considering: (1) the data preference hierarchy in Procedure #5, and (2) the relative uncertainties among trophic level-mean BAFs derived using different methods.

    a. As discussed above, field-measured BAFs and laboratory-measured BCFs are considered equally desirable for deriving a final national BAF using Procedure #5. If a trophic-level-mean BAF is available from both a field-measured BAF and a laboratory-measured BCF, the final national BAF should be selected using the trophic-level-mean BAF with the least overall uncertainty.

    b. The above steps should be performed for each trophic level until a national BAF is selected for trophic levels two, three, and four.

5.6.4 Deriving BAFs Using Procedure #6

This section contains guidance for calculating national BAFs for inorganic and organometallic chemicals using Procedure #6 as shown in Figure 5-1. The types of inorganic and organometallic chemicals for which Procedure #6 is appropriate are those that are considered likely to biomagnify in aquatic food webs (see Section 5.6.1 above). Methylmercury is an example of an organometallic chemical to which Procedure #6 applies. In Procedure #6, two methods are available to derive the national BAF:

- using a BAF from an acceptable field study (i.e., field-measured BAF), or

- predicting a BAF from an acceptable laboratory-measured BCF and a FCM.

Individual BAFs should be determined from field-measured BAFs or laboratory-measured BCFs and FCMs according to the following guidelines.

5.6.4.1 Determining Field-Measured BAFs

1. Field-measured BAFs should be determined using the guidance provided in Section 5.6.3.1 of Procedure #5.

5.6.4.2 Determining Laboratory-Measured BCFs

1. Except where noted below, BAFs should be predicted from laboratory-measured BCFs using the guidance provided in Section 5.6.3.2 of Procedure #5.

2. Because biomagnification is of concern for chemicals applicable to Procedure #6, BAFs should be predicted from laboratory-measured BCF using FCMs. Currently, there are no generic models from which to predict FCMs for inorganic or organometallic chemicals. Therefore, FCMs should be determined using field data as described in the section entitled: "Field-Derived FCMs" in Section 5.4.3.1(c) of Procedure #1. Unlike nonionic organic chemicals, field-derived FCMs for inorganic and organometallic chemicals are not based on lipid-normalized concentrations in tissues. For calculating FCMs for inorganic and organometallic chemicals, concentrations in tissues should be based on the consistent use of either wet-weight or dry-weight concentrations in edible tissues. FCMs should be derived for trophic levels two, three, and four.

5.6.4.3 Determining the National BAF

After calculating individual BAFs using as many of the methods in Procedure #6 as possible, the next step is to determine national BAFs for each trophic level from the individual BAFs. The national BAFs will be used to determine the national 304(a) criteria. The national BAFs should be determined from the individual BAFs by considering the data preference hierarchy defined for Procedure #6 and uncertainty in the data. The data preference hierarchy for Procedure #6 is (in order of preference):

1. a BAF from an acceptable field-measured BAF, or
2. a predicted BAF from an acceptable laboratory-measured BCF and FCM.

This data preference hierarchy reflects EPA's preference for field-measured BAFs over BAFs predicted from a laboratory-measured BCF and FCM, because field-measured BAFs are direct measures of bioaccumulation and biomagnification in aquatic food webs. BAFs predicted from laboratory-measured BCFs and FCMs indirectly account for biomagnification through the use of the FCM. For each trophic level, the national BAFs should be determined using the following steps and guidelines.

1. **Calculate Species-Mean BAFs.** For each BAF method where more than one acceptable field-measured BAF or BAF predicted using a BCF and FCM is available, calculate a species-mean BAF according to the guidance described previously in Procedure #5.

2. **Calculate Trophic Level-Mean BAFs.** For each BAF method where more than one acceptable species-mean BAF is available within a given trophic level, calculate the trophic level-mean BAF according to guidance described previously in Procedure #5.

3. **Select a Final National BAF for Each Trophic Level.** For each trophic level, select the final national BAF using best professional judgment by considering: (1) the data preference hierarchy in Procedure #6, and (2) the relative uncertainties among trophic level-mean BAFs derived using different methods.

    a. When a trophic-level mean BAF is available using both methods for a given trophic level (i.e., a field-measured BAF and a BAF predicted from a BCF and FCM), the national BAF should usually be selected using the field-measured BAF which is the preferred BAF method in the data preference hierarchy in Procedure #6.

    b. If uncertainty in the trophic-level mean BAF derived using field-measured BAFs is considered to be substantially greater than a trophic-level mean BAF derived using a BCF and FCM, the national BAF for that trophic level should be selected from the second tier (BCF · FCM) method.

    c. The above steps should be performed for each trophic level until a national BAF is selected for trophic levels two, three, and four.

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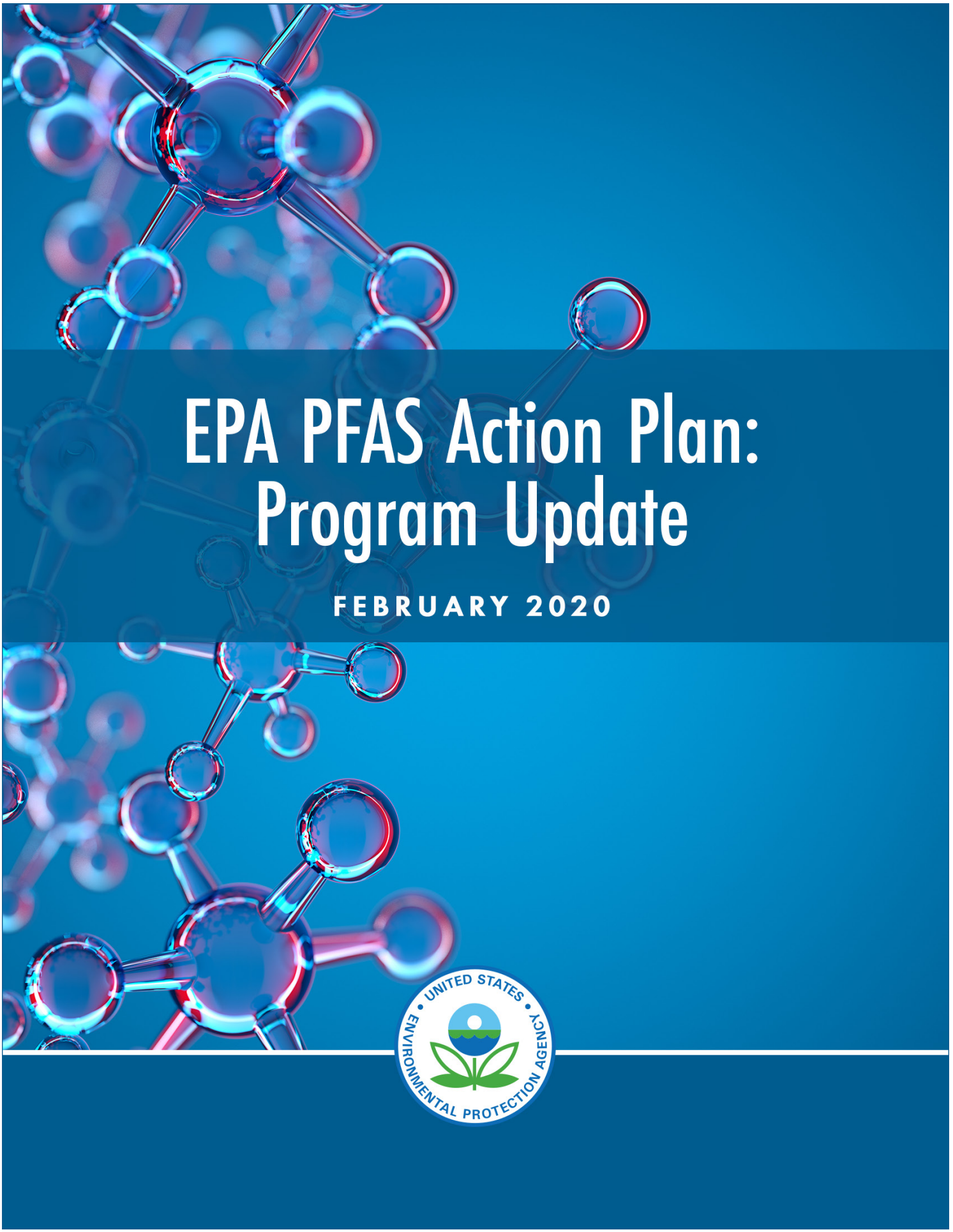
Exhibit 88



EPA PFAS Action Plan: Program Update

FEBRUARY 2020

2020 TR LANL-02039

LETTER FROM THE ADMINISTRATOR

Last year, the U.S. Environmental Protection Agency (EPA) issued the first-ever PFAS Action Plan—a historic step in our nation's efforts to address per- and polyfluoroalkyl substances (PFAS) in the environment. The Action Plan represented a number of important firsts for the agency. It was the first time we have used all of our program offices to deal with an emerging chemical of concern. It was also the first time the agency had put together a multi-media, multi-program national research and risk communication plan to address a challenge like PFAS. By prioritizing our work under the Action Plan, we are delivering on President Trump's commitment to protect the health and well-being of communities across the country that are working to address PFAS.

Over the past year, we have built on the momentum the launch of the PFAS Action Plan put in motion, and our efforts have been nothing short of unprecedented. We have made progress in all of our program areas—from groundwater cleanup guidance, to new test methods that are helping to move our research efforts forward, to updates to our Toxics Release Inventory, to progress on updating our drinking water standards. These actions reflect the comprehensive and coordinated approach we outlined in the PFAS Action Plan; and I want to thank and congratulate the career staff at EPA for their hard work and their unwavering commitment to addressing this issue over the past year.

The Action Plan outlines more than 20 key focus areas that include both short-term and long-term goals. While we are recognizing our accomplishments over the past year, we know we have more work to do. Addressing this challenge will require action from all levels of government—federal, state, local, and tribal, which is why this year I put a new emphasis on identifying funding opportunities for PFAS research and mitigation efforts. In just one year, EPA announced approximately $15 million for new research efforts—including first-of-its-kind funding for the agriculture sector. We also highlighted new ways that our existing programs, like the State Revolving Funds, can be used to address PFAS.

As our regulatory and research efforts mature, I believe it is even more important to enhance the partnerships that we have with other nations; our federal partners; and our own state, local, and tribal governments. Over the past year, we have met with international partners who are using our Action Plan as a guide for efforts in their own countries. We have forged new partnerships and have expanded our technical assistance and support to new states and local communities. Finally, we have taken enforcement actions against companies.

This year EPA is celebrating 50 years of environmental protection. We are celebrating the progress that we've made in setting the nation's air quality standards to protect human health, regulating the quality of public drinking water, creating the Superfund program to clean up hazardous waste sites, and protecting children from exposure to lead-based paint, to name a few. As we look to the future, I look forward to working shoulder-to-shoulder with states, local communities, tribes, water utilities, other federal agencies, and private parties to implement the PFAS Action Plan and continue our progress for a stronger future.

Andrew Wheeler
Administrator

EPA PUBLICATION NUMBER: 100K20002

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2020 TR LANL-02041

INTRODUCTION

EPA Administrator Andrew Wheeler, who is joined by Cosmo Servidio, announces PFAS Action Plan in Philadelphia, Pennsylvania.

Per- and polyfluoroalkyl substances (PFAS) are a group of man-made chemicals that have been manufactured and used by a variety of industries since 1940. Common applications of PFAS include water and stain repellant materials, as well as firefighting products. While the use of certain PFAS have been discontinued, legacy uses and a lack of commercially viable alternatives to certain public safety products (e.g., fire fighting foams) have resulted in PFAS contamination in certain areas.

In May 2018, EPA convened a two-day National Leadership Summit on PFAS that brought together more than 200 federal, state, and local leaders to discuss steps to address PFAS. The Summit set the following goals: evaluate the need for a maximum contaminant level (MCL) for PFOA and PFOS in drinking water, evaluate designating PFOA and PFOS as hazardous substances, issue groundwater cleanup guidances for PFOA and PFOS, and develop toxicity values for GenX and PFBS. Following the Summit, EPA interacted with more than 1,000 people during PFAS-focused community engagement events in Exeter, New Hampshire; Horsham, Pennsylvania; Colorado Springs, Colorado; Fayetteville, North Carolina; and Leavenworth, Kansas as well as through a roundtable in Kalamazoo, Michigan and an event with tribal representatives in Spokane, Washington.

As a result of these meetings and building on the goals identified at the Summit and the approximately 120,000 public comments received by the agency, EPA developed the PFAS Action Plan, which was issued in February 2019. The PFAS Action Plan is the first multi-media, multi-program, national research, management, and risk communication plan to address an emerging contaminant like PFAS. The PFAS Action Plan outlines the tools EPA is developing to, among other things, address PFAS in drinking water, identify and clean up PFAS contamination, expand monitoring of PFAS in manufacturing, increase PFAS scientific research, and exercise effective enforcement tools. The Action Plan outlines EPA's commitment to take a wide variety of actions to address this emerging contaminant in both short-term and long-term timeframes.

Together, these efforts are helping EPA and our partners identify and better understand PFAS contaminants generally, clean up current PFAS contamination, prevent future contamination, and effectively communicate risk with the public. In continuing to implement the PFAS Action Plan, EPA is committed to coordinating closely with multiple entities, including other federal agencies, states, tribes, local governments, water utilities, industry, and the public.

EPA is issuing this report one year after the PFAS Action Plan was released to provide an update on the actions the agency has taken to address PFAS.

2020 TR LANL-02042

UPDATE ON EPA PFAS ACTIONS

Addressing PFAS in Drinking Water

As part of EPA's efforts under the PFAS Action Plan, the agency is following through on its commitment to address PFAS in drinking water. The agency's work over the past year included efforts to expand drinking water test methods, to work under the Safe Drinking Water Act (SDWA) to make a regulatory determination for PFOA and PFOS, to produce new toxicity assessments, and to continue monitoring for PFAS.

Drinking Water Method 533

EPA, along with its federal, state, local, and tribal partners, is working to develop reliable and consistent laboratory methods for detecting and identifying PFAS in drinking water. In December 2019, EPA announced a new validated method for testing additional PFAS in drinking water, EPA Method 533. The new validated test method complements other actions the agency has taken under the Action Plan to help communities address PFAS nationwide. This scientific advancement makes it possible for both government and private laboratories to effectively measure more PFAS chemicals in drinking water than was possible before. EPA's Method 533 focuses on those PFAS with carbon chain lengths of 4 to 12, and complements EPA Method 537.1, published in November 2018. With this new method, the agency can measure 29 chemicals, which marks a critical step under the PFAS Action Plan.

2020 TR LANL-02043

United States Environmental Protection Agency

EPA Analytical Methods for PFAS in Drinking Water

EPA's new validated Method 533 focuses on "short chain" per- and polyfluoroalkyl substances (PFAS) (i.e., those with carbon chain lengths of 4 to 12). Method 533 complements EPA Method 537.1 (published November 2018) and can be used to test for 11 additional PFAS. Using both methods, a total of 29 unique PFAS can be effectively measured in drinking water.

Analyte	Abbreviation	CASRN	Method 533	Method 537.1
11-Chloroeicosafluoro-3-oxaundecane-1-sulfonic acid	11Cl-PF3OUdS	763051-92-9	x	x
9-Chlorohexadecafluoro-3-oxanonane-1-sulfonic acd	9Cl-PF3ONS	756426-58-1	x	x
4,8-Dioxa-3H-perfluorononanoic acid	ADONA	919005-14-4	x	x
Hexafluoropropylene oxide dimer acid	HFPO-DA	13252-13-6	x	x
Perfluorobutanesulfonic acid	PFBS	375-73-5	x	x
Perfluorodecanoic acid	PFDA	335-76-2	x	x
Perfluorododecanoic acid	PFDoA	307-55-1	x	x
Perfluoroheptanoic acid	PFHpA	375-85-9	x	x
Perfluorohexanoic acid	PFHxA	307-24-4	x	x
Perfluorohexanesulfonic acid	PFHxS	355-46-4	x	x
Perfluorononanoic acid	PFNA	375-95-1	x	x
Perfluorooctanoic acid	PFOA	335-67-1	x	x
Perfluorooctanesulfonic acid	PFOS	1763-23-1	x	x
Perfluoroundecanoic acid	PFUnA	2058-94-8	x	x
1H,1H, 2H, 2H-Perfluorohexane sulfonic acid	4:2FTS	757124-72-4	x	
1H,1H, 2H, 2H-Perfluorooctane sulfonic acid	6:2FTS	27619-97-2	x	
1H,1H, 2H, 2H-Perfluorodecane sulfonic acid	8:2FTS	39108-34-4	x	
Nonafluoro-3,6-dioxaheptanoic acid	NFDHA	151772-58-6	x	
Perfluorobutanoic acid	PFBA	375-22-4	x	
Perfluoro(2-ethoxyethane)sulfonic acid	PFEESA	113507-82-7	x	
Perfluoroheptanesulfonic acid	PFHpS	375-92-8	x	
Perfluoro-4-methoxybutanoic acid	PFMBA	863090-89-5	x	
Perfluoro-3-methoxypropanoic acid	PFMPA	377-73-1	x	
Perfluoropentanoic acid	PFPeA	2706-90-3	x	
Perfluoropentanesulfonic acid	PFPeS	2706-91-4	x	
N-ethyl perfluorooctanesulfonamidoacetic acid	NEtFOSAA	2991-50-6		x
N-methyl perfluorooctanesulfonamidoacetic acid	NMeFOSAA	2355-31-9		x
Perfluorotetradecanoic acid	PFTA	376-06-7		x
Perfluorotridecanoic acid	PFTrDA	72629-94-8		x

Office of Water (MS-140) EPA 815-B-19-021 December 2019

2020 TR LANL-02044

Drinking Water Regulatory Determination

EPA is committed to following the Safe Drinking Water Act (SDWA) process for evaluating drinking water standards for two PFAS—PFOA and PFOS. The statutory process involves determining whether:

1) The contaminant may have an adverse effect on the health of persons;

2) The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and

3) In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

In February 2020, EPA announced that it is proposing to regulate both PFOA and PFOS under the SDWA—a critical step as the agency continues its efforts to protect drinking water and public health nationwide. This preliminary determination is a step toward providing state and local communities with key information about PFOA and PFOS in drinking water. In the proposal, EPA is also asking for information and data on other PFAS substances, as well as seeking comment on potential monitoring requirements and regulatory approaches EPA is considering for PFAS chemicals. If the positive regulatory determination is finalized, the agency would begin the process to establish a national primary drinking water regulation for PFOA and PFOS.

Unregulated Contaminant Monitoring Rule 5

The 1996 Safe Drinking Water Act (SDWA) amendments require that once every five years EPA issue a new list of unregulated contaminants to be monitored by public water systems. This data supports the agency's efforts to regulate particular contaminants of potential public health concern. Consistent with recent statutory changes, including the National Defense Authorization Act (NDAA) for Fiscal Year 2020, EPA is committed to monitoring for PFAS in the next Unregulated Contaminant Monitoring Rule (UCMR) cycle. The agency looks forward to issuing a proposed rule this year and working through the regulatory process outlined in the SDWA.

Other Water Actions

Under the PFAS Action Plan, EPA is working to determine if there is enough available data and research to support the development of Clean Water Act (CWA) water quality criteria for PFAS. EPA develops criteria for determining when water has become unsafe for people and wildlife using the latest scientific knowledge. These criteria are recommendations, and state and tribal governments may choose to adopt these criteria or use them as guidance in developing their own water quality criteria. Currently, EPA is scoping development of draft human health and aquatic life criteria for PFOA and PFOS. EPA is also actively collaborating with the Department of Defense to develop benchmarks to protect aquatic life and aquatic-dependent wildlife.

In addition, EPA is developing a risk assessment to better understand the potential public health and ecological risks associated with PFOA and PFOS in land-applied biosolids. Over the past year, EPA has engaged with stakeholders through site visits, webinars, and meetings to gather information on the use of biosolids.

Lastly, EPA is examining available information about PFAS in discharges to surface water to identify industrial sources that may warrant further study for potential regulation. Included in EPA's Preliminary Effluent Guidelines Plan 14 is initial analyses of industrial sources and discharges of PFAS. This information is part of a multi-industry study to determine which industries are most likely to discharge PFAS into the environment and to determine the specific PFAS compounds currently in use.

2020 TR LANL-02045

Reducing PFAS Exposure through Cleanups

EPA supports its federal, state, local, and tribal partners by providing assistance in efforts to identify exposures, develop methods to measure PFAS in the environment, and support cleanup efforts where PFAS chemicals have been identified as a risk to public health. EPA is currently providing cleanup assistance to more than 30 states and the District of Columbia to address PFAS contamination. Over the past year, EPA has made considerable progress under the PFAS Action Plan as it relates to clean ups.

Administrator Andrew Wheeler tours a Superfund site.

Groundwater Guidance for Federal Clean Up Programs

In December 2019, EPA met its own deadline to issue Interim Recommendations for Addressing Groundwater Contaminated with PFOA and PFOS under federal cleanup programs, a priority action under the PFAS Action Plan. The interim recommendations provide clear and consistent guidance for federal cleanup programs and help protect drinking water resources in communities across the country. This is a critical tool for the agency's state, tribal, and local partners to use to protect public health and address these chemicals.

"We welcome the EPA's release of the Interim Recommendations for Addressing Groundwater Contaminated with PFOA/PFAS under federal cleanup programs," said the Association of State and Territorial Solid Waste Management Officials (ASTSWMO).

With these interim recommendations, EPA is prioritizing public health impacts by focusing on addressing groundwater that is a current or potential source of drinking water. The guidance recommends:

- Using a screening level of 40 parts per trillion (ppt) to determine if PFOA and/or PFOS is present at a site and may warrant further attention.
    - Screening levels are risk-based values that are used to determine if levels of contamination may warrant further investigation at a site.
- Using EPA's PFOA and PFOS Lifetime Drinking Water Health Advisory level of 70 ppt as the preliminary remediation goal (PRG) for contaminated groundwater that is a current or potential source of drinking water, where no state or tribal MCL or other applicable or relevant and appropriate requirements (ARARs) are available or sufficiently protective.
    - PRGs are generally initial targets for cleanup, which may be adjusted on a site-specific basis as more information becomes available.

After reviewing public comments on the agency's April 2019 draft guidance, EPA finalized the interim recommendations based on the available data and scientific information on PFAS toxicity. EPA acknowledges that the scientific information on these compounds is continuing to evolve. As part of the PFAS Action Plan, EPA continues to develop and assess toxicity information, test methods, laboratory methods, analytical methods, exposure models, and treatment methods, among other research efforts to improve the agency's knowledge about this class of chemicals. As new information becomes available on other PFAS chemicals, the agency will consider additional recommendations.

2020 TR LANL-02046

CERCLA Hazardous Substance Designation

Helping other federal agencies, cities, states, and tribes address legacy PFAS contamination at Superfund sites and other federal cleanup sites is one of the agency's top priorities under the PFAS Action Plan. In 2019, EPA continued to provide technical assistance on site-specific PFAS challenges across the country, including using the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and other authorities, as appropriate, to investigate sites. Along with EPA's work on the interim groundwater cleanup recommendations issued in 2019, the agency continued moving forward with the regulatory process for proposing to designate PFOA and PFOS as hazardous substances under CERCLA.

Analytical Methods for Other Environmental Media

In addition to test methods for drinking water, EPA worked to develop test methods for PFAS in non-potable groundwater, surface water, and wastewater. The agency issued for public comment SW-846 Method 8327, a multi-lab validated method that is used to conduct assessments and develop remediation treatment technologies and disposal practices. EPA accepted comments through August 2019 on the published method. The agency is continuing to review those comment in its efforts to revise the methods for future publication in the SW-846 compendium in 2020.

Treatment and Disposal Research

The agency also has numerous PFAS treatment and disposal research projects underway, including on high temperature incineration and other methods. The agency is collaborating with other federal partners, including the Department of Defense, on efforts to increase the agency's understanding and availability of treatment technologies for PFAS, including analytical methods. Under the NDAA for Fiscal Year 2020, EPA will work to publish interim guidance on the destruction and disposal of PFAS within one year and publish revisions every three years after that.

Ensuring Safety and Understanding PFAS in Commerce: EPA Actions Under the Toxics Release Inventory and the Toxic Substances Control Act

EPA is responsible for reviewing new chemical substances before they enter commerce to help manage the potential risk to public health and the environment from chemicals that are new to the marketplace. Since 2000, EPA has reviewed hundreds of new PFAS chemicals. In many cases, the agency used its authority under the Toxic Substances Control Act (TSCA) to impose restrictions on these substances. The agency has also used its authority to require companies to provide data on chemical properties, toxicity, and other health effects information. EPA has expanded on these efforts under the PFAS Action Plan, including the agency's work to update the Toxics Release Inventory program to include PFAS and efforts to finalize a Significant New Use Rule for PFAS chemicals.

2020 TR LANL-02047

The Toxics Release Inventory

EPA continues to receive, review, and take appropriate risk management actions for new PFAS chemicals received through Pre-Manufacture Notices and Low Volume Exemption Notices. For both types of notices, EPA conducts a full life-cycle risk assessment for the chemical under the conditions of use.

In November 2019, EPA announced a 60-day public comment period on potentially adding certain per- and polyfluoroalkyl substances (PFAS) to the list of chemicals that companies are required to report to the agency as part of the Toxics Release Inventory (TRI). Exploring the addition of certain PFAS chemicals to the TRI is an important step that will provide information to the public on these chemicals for the first time. The information gathered through this advance notice of proposed rulemaking (ANPRM) will be used for two purposes:

- First, the public input will help the agency determine whether data and information are available to fulfill the TRI chemical listing criteria.
- Second, EPA will use the input to help evaluate the extent and utility of the data that would be gathered under the TRI.

In a separate but related effort, on December 31, 2019, EPA notified TRI reporters that facilities need to track and collect data on PFAS chemicals during 2020, a new requirement included in the FY 2020 NDAA. To provide clear information on which chemicals fall under the NDAA requirement, in February 2020, EPA released a list of 172 PFAS chemicals that are subject to TRI reporting. The NDAA also instructs EPA to consider adding additional PFAS to the TRI chemical list. While the NDAA adds certain PFAS to the TRI chemical list, there are additional PFAS that were not added by the NDAA. Through the ANPRM announced in November 2019, EPA solicited comments on PFAS generally as they relate to TRI reporting, including comment on appropriate reporting thresholds, categorization of PFAS, availability of information on human health and environmental toxicity, persistence, and bioaccumulation of these additional PFAS that would help determine if they meet listing criteria.

EPA's TRI program is an important tool that provides the public with information about chemical releases and pollution prevention activities reported by industrial and federal facilities. U.S. facilities in different industry sectors must report annually how much of each chemical is released to the environment and/or managed through recycling, energy recovery, and treatment. TRI reporting requirements state that a facility should use readily available data collected pursuant to other provisions of law or, where such data are not readily available, reasonable estimates of the amounts involved. Reporting on the recently added PFAS will be due by July 1, 2021, for 2020 data including the PFAS added to the TRI by the NDAA. TRI information helps support informed decision-making by companies, government agencies, non-governmental organizations and the public.

Significant New Use Rule

Of the more than 600 PFAS chemicals on the active TSCA inventory, EPA has reviewed almost 60 percent of them under the new chemicals program. Since 2006, the agency has reviewed around 300 PFAS new chemical notices and has regulated about 200 with consent orders and/or new chemical SNURs.

In 2015, EPA proposed a Significant New Use Rule (SNUR) for long-chain PFAS that would require manufacturers (including importers) of PFOA and certain PFOA-related chemicals to notify EPA at least 90 days before starting or resuming manufacture (including import) or processing for new uses of these chemicals in any products. In February 2020, EPA issued a supplemental proposal that strengthens regulations on imported products containing these chemicals in surface coatings. This supplemental proposal, once final, would require EPA to review new uses of imported products containing certain PFAS as a surface coating. EPA's 2020 proposal supplements parts of the 2015 proposed rule on PFAS imports by clarifying the categories of products that would be covered. When finalized, this rule would ensure that uses which are phased out in products like furniture, automobile parts, electronics, and household appliances that could contain these PFAS chemicals as a surface coating cannot be imported to the U.S. unless EPA reviews the new uses and puts in place the necessary restrictions to address any unreasonable risks. This action would close an important loophole that currently allows products containing certain PFAS chemicals that have been phased out in the United States to still be imported into the United States. It also would level the playing field for companies that have already voluntarily phased-out the use of long-chain PFAS chemicals under EPA's PFOA Stewardship Program by preventing new uses of these phased-out chemicals to begin again.

2020 TR LANL-02048

Increasing Research to Reduce Risks

The science needed to protect public health and the environment from PFAS exposure cuts across many applications and disciplines. EPA's goal under the PFAS Action Plan is to develop and apply scientific information and tools to enable federal, state, local, and tribal governments to work together to make informed decisions to protect public health and the environment. Some of EPA's key research accomplishments over the past year include the following.

PFAS in Agriculture and Rural Communities

In February 2019, Administrator Wheeler directed the Office of Research and Development to "generate practical and actionable science to help manage PFAS chemical issues impacting agriculture and rural economies." Under this effort EPA has established a robust workgroup with the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) on PFAS analytical methods for agricultural and food products. The group is also collaborating with USDA on modeling PFAS in contaminated dairy cows. EPA is contributing to USDA's efforts under the 2019 Farm Bill to support environmental remediation in rural American, which includes addressing PFAS.

Analytical Methods R&D

There are hundreds of different PFAS chemicals of varying sizes and lengths and sampling. Analyzing them in a comprehensive way has been a challenge that scientists at all levels of government are working to address. EPA has published new test methods for drinking water, and is continuing to work on methods for groundwater, surface water, and wastewater. The agency has also developed research methods for measuring PFAS in human serum and urine, and estuarine water. The agency is also working to develop and apply high-resolution mass spectrometry techniques to conduct Non-Targeted Analysis of PFAS in the environment, which is a critical step in the agency's efforts to comprehensively address these chemicals. Finally, EPA is working to develop sampling and analytical methods for detecting and measuring PFAS in stack emissions.

Toxicity and Effects R&D

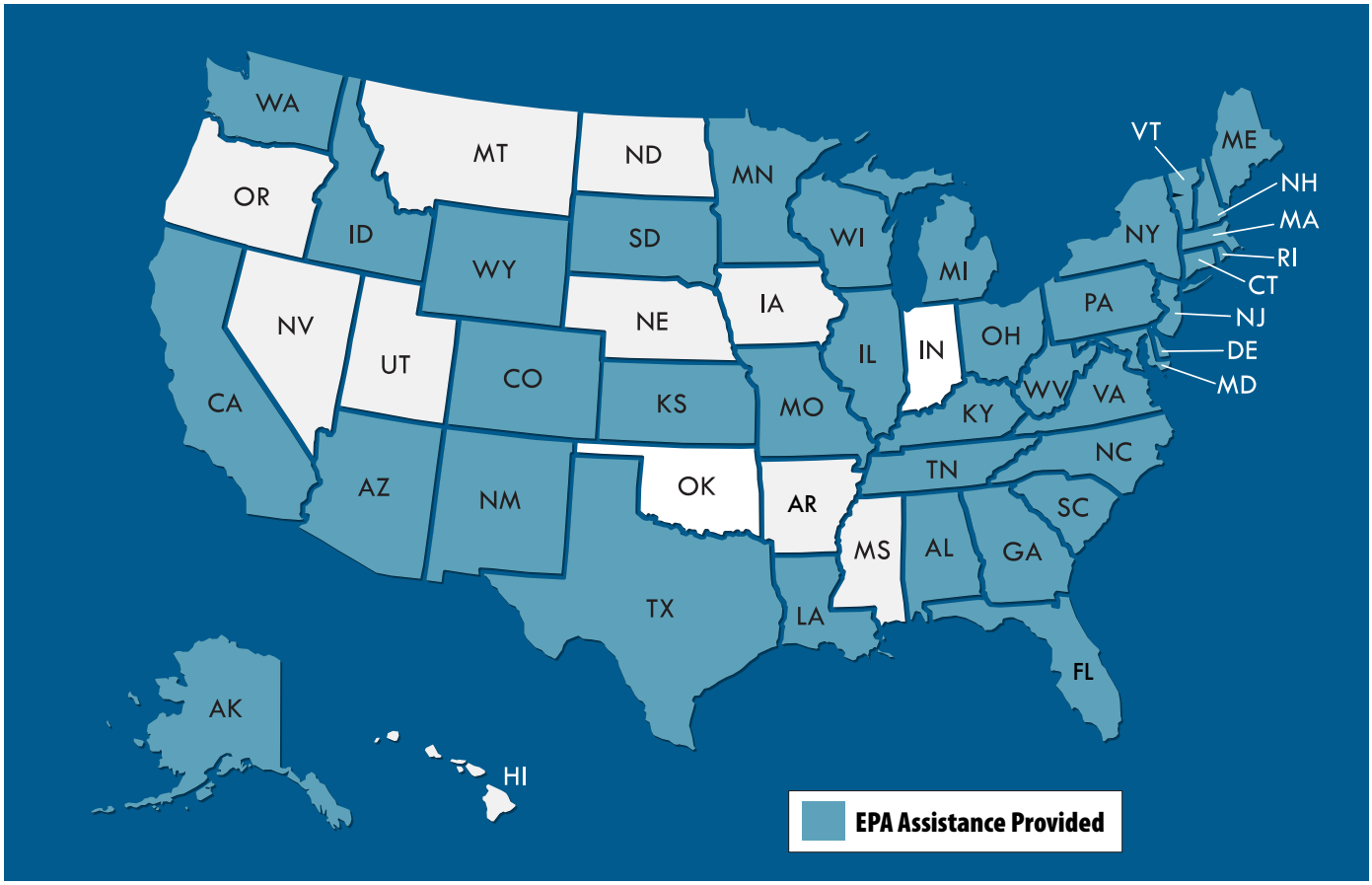
EPA is currently researching the human health effects of seven of the most common PFAS. In 2019, EPA sought public input on draft toxicity assessments for GenX chemicals and perfluorobutane sulfonic acid (PFBS). To develop these draft toxicity assessments, the agency relied on the best available science, including input from independent peer reviewers. The agency also engaged with federal and state partners throughout the development of the draft assessments. For GenX, EPA has collaborated with a National Toxicology Program expert panel to review the toxicological study to address key technical comments received on the proposed toxicity assessments issued in 2018. The expert panel issued their report in 2019 and the agency looks forward to finalizing the assessment in 2020. EPA expects to finalize the PFBS and GenX toxicity assessments in 2020 and will continue working closely with all of its partners as the agency works to consider public input and revise these assessments.

Further, EPA is conducting an Integrated Risk Information System (IRIS) assessment on perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluorohexanoic acid (PFHxA), perfluorohexanesulfonate (PFHxS), and perfluorobutanoic acid (PFBA). The IRIS assessments will identify the potential human health effects from exposure to each assessed PFAS and will develop toxicity values, as supported by the available evidence. The assessments will evaluate both cancer and noncancer effects, including potential effects on the endocrine, hepatic, urinary, immune, developmental, and reproductive systems. EPA expects to propose draft toxicity values of these chemicals for public and scientific review in 2020.

2020 TR LANL-02049

Expanding Technical Assistance, Enforcement, and Support

Over the past year, EPA provided technical support to multiple states on PFAS contamination and treatment. EPA is currently responding to requests for assistance from more than a dozen state and territorial governments by screening for PFAS at high priority sites and training local health agencies to test for PFAS on their own. EPA is also providing cleanup assistance to more than 30 states and the District of Columbia to address PFAS at contaminated groundwater and soil sites. For example, at the request of the State of North Carolina, in 2017 and 2018 EPA provided significant laboratory assistance to support the State's investigation of GenX in the Cape Fear River, which resulted in a state enforcement action and February 2019 state settlement.



EPA is providing assistance to states across the United States.

2020 TR LANL-02050

Effective Enforcement

EPA has taken—and will continue to take—enforcement action, as appropriate, to address PFAS to protect human health and the environment. For example, EPA took an enforcement action in 2019 against facilities in West Virginia and North Carolina for violating requirements under the TSCA while manufacturing PFAS chemicals. In October 2019, in coordination with Michigan Department of Environment, Great Lakes, and Energy, EPA issued an administrative consent order under CERCLA to Wolverine World Wide, Inc. to complete removal action work related to their Michigan facility that has both hazardous substance and PFAS contamination.

Since 2002, the agency has initiated 12 enforcement actions, including four since 2017. EPA will continue to partner with states on compliance assistance and enforcement, as necessary. The agency is also continuing to investigate PFAS releases, including issuing 20 information request letters and conducting 11 onsite inspections since July 2017, including joint inspections with states.

- Specifically, EPA has issued a number of information requests regarding PFAS, including:
    - Five CWA information request letters since November 2018 regarding discharges of PFAS from manufacturing or processing facilities,
    - Thirteen TSCA information request letters since January 2018,
    - One CERCLA information request letter in November 2017, and
    - One Resource Conservation and Recovery Act (RCRA) information request letter in April 2018.
- EPA's Office of Enforcement and Compliance Assurance (OECA), with support from its National Enforcement Investigations Center and Regional enforcement divisions, has carried out 11 inspections at eight PFAS manufacturing or processing facilities since July 2017, under the authority of TSCA, CWA, and/or RCRA, including joint inspections with states.
- The agency has multiple criminal investigations underway concerning PFAS-related pollution.

EPA's regional offices are also assisting their states to address PFAS releases and contamination with technical and enforcement support, including joint-prosecution agreements, investigations, inspections, and sampling.

In addition, EPA oversees PFAS response actions by federal agencies at National Priorities List sites. For example, EPA actively engaged with the Army regarding their decision to provide the Town of Ayer, Massachusetts, with a treatment system for well water threatened by a PFAS plume emanating from the former Fort Devens Army base (now a BRAC facility). In February 2019, the Army agreed to take a CERCLA Time Critical Removal Action (TCRA) to address groundwater contamination above the Health Advisory. The TCRA committed Army to eliminate the ongoing discharge of PFAS-contaminated water into surface water and fund installation of a drinking water treatment system to address PFAS contamination in the public drinking water supply.

Information on EPA's federal agency compliance assistance is available on the FedCenter website where federal agency PFAS contacts can share information and find resources.

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PFAS in Air

Under the PFAS Action Plan, EPA is working to better characterize and understand the environmental impacts of PFAS emitted to the air. This work will build on the scientific foundation that has been established to develop sampling and measurement methods for PFAS in air, assess effectiveness of PFAS disposal methods, and understand the efficacy of emission control technology. EPA also has provided support to states on technical matters on destruction and incineration of PFAS in contaminated waste and materials.

Tribal and International Support

EPA has provided robust support to both the tribal and international communities. In Indian Country, tribes are impacted in a number of different ways including their proximity to airports, military bases, industrial facilities, landfills, and past fires. Through its efforts the agency has met with tribes and with representatives from the European Union, Finland, the Netherlands, Germany, Norway, Denmark, Australia, and Japan. The agency's PFAS Action Plan has provided these partners with a roadmap to addressing PFAS within their own countries and in Indian Country. The interactions have also provided opportunities for the agency to learn about the actions other countries are taking to address PFAS.

Funding for Additional PFAS Efforts

As a leader in the nation's efforts to address PFAS in the environment, EPA recognizes that providing funding to external organizations is a critical component to successfully addressing these chemicals. Some of the agency's funding efforts include the following.

Ecological Exposure

In May 2019, EPA awarded approximately $3.9 million through two grants for research that will improve understanding of human and ecological exposure to PFAS in the environment. The research will also promote a greater awareness of how to restore water quality in PFAS-impacted communities.

- The Colorado School of Mines in Golden, Colorado will research the fate, transport, bioaccumulation, and exposure of a diverse suite of PFAS in nationally representative PFAS impacted communities.
- Oregon State University in Corvallis, Oregon will study the toxicity of a large collection of PFAS and PFAS mixtures with the zebrafish assay and mice studies to identify toxic PFAS that require prioritization for risk management.

Environmental Risks in Waste

In September 2019, EPA also awarded nearly $6 million to fund research by eight organizations to expand the understanding of the environmental risks posed by PFAS in waste streams and to identify practical approaches to manage the potential impacts as PFAS enters the environment. Funding was awarded to:

- New York State Department of Health - Health Research Inc., Menands, N.Y. – to build a dataset by analyzing samples from approximately 150 landfills in the State of New York. This data will be used to understand the types and concentrations of PFAS that are found in and around landfills, as well as the key landfill attributes that contribute to release of PFAS.

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- North Carolina State University, Raleigh, N.C. – to collect landfill gas (LFG) samples from over 400 landfills across the U.S. to determine if PFAS from LFG is a significant source of PFAS released into the atmosphere.
- University of Florida, Gainsville, Fla. – to study the role of waste type, management strategies, and treatment methods on the occurrence, source and fate of PFAS in landfills. The study will identify the sources of PFAS compounds in the current domestic waste stream using laboratory-scale batch leaching, and landfill simulation studies.
- Clemson University, Clemson, S.C. – to examine the chemical process for the destruction of PFAS in leachate and groundwater. This project will assess degradation kinetics, test hypothesized process modifications, and conduct trials of leachate treatment.
- Purdue University, West Lafayette, Ind. – to develop methods to decrease PFAS concentrations in both municipal wastewater treatment plant effluent and sludge. The study will determine the technical and economic feasibility of using a treatment approach consisting of nanofiltration followed by electrochemical oxidation.
- Texas A&M AgriLife Research, College Station, Texas – to investigate the feasibility of electron beam technology for the destruction of PFAS compounds during the remediation of groundwater, wastewater, sewage sludges, and soils.
- Texas Tech University, Lubbock, Texas – to identify and quantify the occurrence of PFAS in landfill leachate, investigate the fate of PFAS passing through typical landfill liner systems, and test the ability to break down PFAS in landfill leachate using soundwaves.
- University of North Dakota, Grand Forks, N.D. – to develop practical strategies for removing legacy and emerging PFAS from leachate and groundwater by studying the adsorption, desorption, and biodegradation of PFAS and precursor compounds in landfills.

PFAS in Agriculture

In November 2019, EPA announced the availability of nearly $5 million for new research on PFAS in agriculture, which will help fulfill Administrator Wheeler's call for the agency to prioritize new federal research that will help farmers, ranchers, and rural communities.

"NASDA appreciates the EPA's efforts to prioritize PFAS research that will help the agricultural community. As the primary stewards for the agricultural industries in their states, NASDA members will continue to work closely with the EPA as the agency implements its PFAS Action Plan. Together, we can ensure healthy communities and farms across America," **said National Association of State Departments of Agriculture (NASDA) CEO Dr. Barbara P. Glenn.**

"EPA is uniquely suited to lead and promote research on this important topic and USDA applauds EPA's focus on farmers, ranchers, and rural communities. EPA's funding of this research complements the work USDA does supporting U.S. production agriculture and ensuring a safe food supply," **said USDA Deputy Under Secretary for Research, Education, and Economics Dr. Scott Hutchins.**

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PFAS Under the Drinking Water State Revolving Fund (DWSRF)

The DWSRF can provide financial assistance to publicly-owned and privately-owned community water systems, as well as non-profit non-community water systems, for drinking water infrastructure projects. Projects must either facilitate the system's compliance with national primary drinking water regulations or significantly further the health protection objectives of the Safe Drinking Water Act. Infrastructure needs related to addressing PFAS are eligible projects. Examples of projects could include funding equipment, such as laboratory equipment, upgrading treatment technologies to add PFAS removal capability, and funding routine training for system operators.

Risk Communications and Engagement

Risk communication and engagement are critical for EPA to effectively support communities across the United States that are addressing PFAS. As outlined in the PFAS Action Plan, EPA is actively working to enhance the way in which the agency communicates about potential human health risks that may be associated with PFAS.

At the National Leadership Summit and throughout the public engagement sessions the agency held across the country, EPA heard that it is important to clearly explain the actions the agency is taking as well as the specific concerns that those actions are intended to address. Throughout the past year, the agency has consistently worked to ensure that both of those goals were met. Through press releases, public speaking engagements, congressional testimony, social media, and on www.epa.gov, the agency is ensuring that its voice is clearly articulated in the public discourse as it relates to these chemicals. EPA's actions, and the corresponding communications products, show EPA's robust, comprehensive and collaborative approach to accurately and appropriately communicate risk to the public.

EPA Administrator Wheeler has made risk communications a priority for the agency since he became Administrator. Over the past year, EPA has worked to expand its risk communications efforts internally, which include a strong focus on PFAS. Over the next year, the agency looks forward to rolling out new materials; continuing to coordinate with our federal, state, local, and tribal partners to ensure consistent messaging; and adding training opportunities for the agency's workforce. Together, these efforts will help the agency enhance the public's understanding of the potential health effects associated with PFAS and provide support to all the agency's partners.

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CONCLUSION

EPA is committed to continuing to aggressively implement the PFAS Action Plan—the most comprehensive cross-agency plan ever to address an emerging chemical of concern. EPA's Action Plan and the progress that has been made over the past year under the Plan demonstrates the agency's leadership role at the national level to address this emerging environmental concern. This includes ensuring that instances where PFAS pose risk to public health or the environment are identified and quickly addressed. The agency looks forward to continued progress both within and outside of the agency. Over the next year, EPA will make progress on addressing PFAS under the Safe Drinking Water Act, the Comprehensive Environmental Response, Compensation, and Liability Act, the Resource Conservation and Recovery Act, and the Toxic Substances Control Act. The agency will also work to expand its research efforts as well as enhance the agency's engagement with the rest of the federal government. The agency will also focus its efforts on providing more information and data to the public.

"For the first time in Agency history, we utilized all of our program offices to construct an all-encompassing plan to help states and local communities address PFAS and protect our nation's drinking water. We have moved forward, and continue to forward, with several important actions, including the maximum contaminant level process, that will help affected communities better monitor, detect, and address PFAS."

EPA Administrator Andrew Wheeler

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UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY

Exhibit 89

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 141

[EPA–HQ–OW–2019–0583; FRL–10005–88–OW]

Announcement of Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List

AGENCY: Environmental Protection Agency (EPA).

ACTION: Request for public comment.

SUMMARY: The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Environmental Protection Agency (EPA) to make regulatory determinations every five years on at least five unregulated contaminants. A regulatory determination is a decision about whether or not to begin the process to propose and promulgate a national primary drinking water regulation (NPDWR) for an unregulated contaminant. A preliminary regulatory determination lays out and takes comment on EPA's view about whether certain unregulated contaminants meet three statutory criteria. After EPA considers public comment, EPA makes a final determination. The unregulated contaminants included in a regulatory determination are chosen from the Contaminant Candidate List (CCL), which the SDWA requires the EPA to publish every five years. The EPA published the fourth CCL (CCL 4) in the **Federal Register** on November 17, 2016. This document presents the preliminary regulatory determinations and supporting rationale for the following eight of the 109 contaminants listed on CCL 4: Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), 1,1-dichloroethane, acetochlor, methyl bromide (bromomethane), metolachlor, nitrobenzene, and Royal Demolition eXplosive (RDX). The Agency is making preliminary determinations to regulate two contaminants (*i.e.,* PFOS and PFOA) and to not regulate six contaminants (*i.e.,* 1,1-dichloroethane, acetochlor, methyl bromide, metolachlor, nitrobenzene, and RDX). The EPA seeks comment on these preliminary determinations. The EPA is also presenting an update on three other CCL 4 contaminants (strontium, 1,4-dioxane, and 1,2,3-trichloropropane).

DATES: Comments must be received on or before May 11, 2020.

ADDRESSES: You may send comments, identified by Docket ID No. EPA–HQ–OW–2019–0583, by any of the following methods:

- *Federal eRulemaking Portal: https://www.regulations.gov/* (our preferred method). Follow the online instructions for submitting comments.
- *Mail:* Water Docket, Environmental Protection Agency, Mail Code: [28221T], 1200 Pennsylvania Ave. NW, Washington, DC 20460.
- *Hand Delivery:* EPA Docket Center, [EPA/DC] EPA West, Room 3334, 1301 Constitution Ave. NW, Washington, DC. Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Instructions: All submissions received must include the Docket ID No. for this rulemaking. Comments received may be posted without change to *https://www.regulations.gov/,* including any personal information provided. For detailed instructions on sending comments and additional information on the rulemaking process, see the ''Written Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

FOR FURTHER INFORMATION CONTACT: Richard Weisman, Standards and Risk Management Division, Office of Ground Water and Drinking Water, MC: 4607M, Environmental Protection Agency, 1200 Pennsylvania Ave. NW; telephone number: (202) 564–2822; email address: *weisman.richard@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Written Comments

Submit your comments, identified by Docket ID No. EPA–HQ–OW–2019–0583, at *https://www.regulations.gov* (our preferred method), or the other methods identified in the **ADDRESSES** section. Once submitted, comments cannot be edited or removed from the docket. The EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.,* on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit *https://www.epa.gov/dockets/commenting-epa-dockets.*

When submitting comments, remember to:

- Identify the rulemaking by docket number and other identifying information (subject heading, **Federal Register** date, and page number).
- Explain why you agree or disagree and suggest alternatives.
- Describe any assumptions and provide any technical information and/or data that you used.
- Provide specific examples to illustrate your concerns and suggest alternatives.
- Explain your views as clearly as possible.
- Make sure to submit your comments by the comment period deadline identified.

B. Does this action apply to me?

Neither these preliminary regulatory determinations nor the final regulatory determinations, when published, impose any requirements on anyone. Instead, this action notifies interested parties of the EPA's preliminary regulatory determinations for eight unregulated contaminants for comment.

Abbreviations Used in This Document

Abbreviation	Meaning
ADAF	Age Dependent Adjustment Factor
ADONA	4,8-dioxa-3H-perfluorononanoic acid
ALT	Alanine Aminotransferase
AM	Assessment Monitoring
AOP	Advanced Oxidative Process
ASDWA	Association of State Drinking Water Administrators
ATSDR	Agency for Toxic Substances and Disease Registry
AWIA	America's Water Infrastructure Act
BAT	Best Available Technology
BMD	Benchmark Dose
BMDL	Benchmark Dose Level
BMDS	Benchmark Dose Software
BMR	Benchmark Response
BW	Body Weight
CAR	Constitutive Androstane Receptor
CBI	Confidential Business Information
CCL	Contaminant Candidate List
CCL 1	First Contaminant Candidate List
CCL 2	Second Contaminant Candidate List
CCL 3	Third Contaminant Candidate List
CCL 4	Fourth Contaminant Candidate List
CDPHE	Colorado Department of Public Health and Environment
CDR	Chemical Data Reporting
CIIT	Chemical Industry Institute of Toxicology
CNS	Central Nervous System
cPAD	Chronic Population Adjusted Dose
CRL	Cancer Risk Level
CSF	Cancer Slope Factor

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Abbreviation	Meaning
CWS	Community Water System
CWSS	Community Water System Survey
D/DBP	Disinfectants/Disinfection Byproducts
DBP	Disinfection Byproduct
DDE	1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene
DWI	Drinking Water Intake
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-To-Know Act
EPTC	S-Ethyl dipropylthiocarbamate
ESA	Ethanesulfonic Acid
FtOH 6:2	6:2 Fluorotelomer Alcohol
FtOH 8:2	8:2 Fluorotelomer Alcohol
FtS 6:2	6:2 Fluorotelomer Sulfonic Acid
FtS 8:2	8:2 Fluorotelomer Sulfonic Acid
FQPA	Food Quality Protection Act
FR	Federal Register
HA	Health Advisory
HDL	High-Density Lipoprotein
HED	Human Equivalent Dose
HERO	Health and Environmental Research Online
HESD	Health Effects Support Document
HFPO	Hexafluoropropylene Oxide
HHRA	Human Health Risk Assessment
HRL	Health Reference Level
IARC	International Agency for Research on Cancer
ICR	Information Collection Rule
IOC	Inorganic Compound
IRED	Interim Reregistration Eligibility Decision
IRIS	Integrated Risk Information System
IUR	Inventory Update Reporting
K_H	Henry's Law Constant
K_{oc}	Organic Carbon Partitioning Coefficients
LOAEL	Lowest Observed Adverse Effect Level
log K_{ow}	Octanol-Water Partitioning Coefficient
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
metHB	Methemoglobin
MOA	Mode of Action
MRL	Minimum Reporting Level
NAM	New Approach Method
NAS	National Academy of Sciences
NAWQA	National Water Quality Assessment
NCDEQ	North Carolina Department of Environmental Quality
NCFAP	National Center for Food and Agricultural Policy
NCI	National Cancer Institute
NDEA	N-Nitrosodiethylamine
NDMA	N-Nitrosodimethylamine
NDPA	N-Nitroso-di-n-propylamine
NDPhA	N-Nitrosodiphenylamine
NDWAC	National Drinking Water Advisory Council
NEtFOSAA	2-(N-Ethylperfluorooctanesulfonamido) acetic acid
NHDES	New Hampshire Department of Environmental Services
NIEHS	National Institute of Environmental Health Sciences
NIRS	National Inorganics and Radionuclides Survey
NMeFOSAA	2-(N-Methylperfluorooctanesulfonamido) Acetic Acid
NOAEL	No Observed Adverse Effect Level
NPDWR	National Primary Drinking Water Regulation
NPYR	N-Nitrosopyrrolidine
NRC	National Research Council
NTP	National Toxicology Program
NWIS	National Water Information System
OA	Oxanilic Acid
OPP	Office of Pesticides Program
ORD	Office of Research and Development
OTC	Ornithine Carbamoyl Transferase
OW	Office of Water
PCCL	Preliminary Contaminant Candidate List
PDP	Pesticide Data Program
PFAA	Perfluorinated Alkyl Acids
PFAS	Per- and Polyfluoroalkyl Substances
PFBA	Perfluorobutanoic Acid
PFBS	Perfluorobutanesulfonic Acid
PFDA	Perfluorodecanoic Acid
PFDS	Perfluorodecanesulfonic Acid
PFHpA	Perfluoroheptanoic Acid
PFHpS	Perfluoroheptanesulfonic Acid
PFHxA	Perfluorohexanoic Acid
PFHxS	Perfluorohexanesulfonic Acid
PFNA	Perfluorononanoic Acid
PFNS	Perfluorononanesulfonic Acid
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctanesulfonic Acid
PFOSA	Perfluorooctanesulfonamide
PFPeA	Perfluoropentanoic Acid
PFPeS	Perfluoropentanesulfonic Acid
PFTeDA	Perfluorotetradecanoic Acid
PFUnA	Perfluoroundecanoic Acid
PMP	Pesticide Monitoring Program
POD	Point of Departure
PPRTV	Provisional Peer-Reviewed Toxicity Value
PST	Pre-Screen Testing
PWS	Public Water System
QA	Quality Assurance
RD 1	Regulatory Determination 1
RD 2	Regulatory Determination 2
RD 3	Regulatory Determination 3
RD 4	Regulatory Determination 4
RDX	Royal Demolition eXplosive
RED	Reregistration Eligibility Decision
RfD	Reference Dose
RSC	Relative Source Contribution
SD	Standard Deviation
SDWA	Safe Drinking Water Act
SS	Screening Survey
SSCT	Small System Compliance Technology
STORET	Storage and Retrieval Data System
TOF	Total Organic Fluorine
TOP	Total Organic Precursor
TPTH	Triphenyltin Hydroxide
TRED	Tolerance Reassessment Progress and Risk Management Decision
TRI	Toxic Release Inventory
TSCA	Toxic Substances Control Act
TT	Treatment Technique
UCM	Unregulated Contaminant Monitoring
UCMR	Unregulated Contaminant Monitoring Rule
UCMR 1	First Unregulated Contaminant Monitoring Rule
UCMR 2	Second Unregulated Contaminant Monitoring Rule
UCMR 3	Third Unregulated Contaminant Monitoring Rule
UF	Uncertainty Factor
UNEP	United Nations Environmental Programme
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	Volatile Organic Compound
WHO	World Health Organization
WQP	Water Quality Portal
WQX	Water Quality Exchange
5:3 acid	2H,2H,3H,3H-Perfluorooctanoic acid
6:2 diPAP	Bis[2-(perfluorohexyl)ethyl] phosphate
6:2 monoPAP	Mono[2-(perfluorohexyl)ethyl] phosphate
6:2/8:2 diPAP	6:2/8:2 Fluorotelomer phosphate diester
8:2 diPAP	Bis[2-(perfluorooctyl)ethyl] phosphate
8:2 monoPAP	Mono[2-(perfluorooctyl)ethyl] phosphate

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II. Purpose and Background

This section briefly summarizes the purpose of this action, the statutory requirements, and previous activities related to the CCL and regulatory determinations.

A. What is the purpose of this action?

The purpose of this action is to request comment on the Environmental Protection Agency's (EPA's) preliminary regulatory determinations for the following eight unregulated contaminants: Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), 1,1-dichloroethane, acetochlor, methyl bromide (bromomethane), metolachlor, nitrobenzene, and RDX. The Agency is making preliminary determinations to regulate two contaminants (PFOS and PFOA) and to not regulate the remaining six contaminants (1,1-dichloroethane, acetochlor, methyl bromide, metolachlor, nitrobenzene, and RDX). As described in Section III.A.3, if the EPA finalizes these preliminary regulatory determinations, it would represent the beginning of the Agency's regulatory development process, not the end. As required by SDWA, the EPA seeks comment on these preliminary determinations and is asking for information and comment on other per- and polyfluoroalkyl substances (PFAS) and potential regulatory approaches. The Agency is also requesting comment on the process and analyses used for this round of regulatory determinations (*i.e.,* RD 4), the supporting information, additional studies or sources of information the Agency should consider, and the rationale used to make these preliminary decisions. The EPA is also presenting an update on strontium (from the third regulatory determination) and two other CCL 4 contaminants for which the Agency is not making preliminary determinations today (1,4-dioxane and 1,2,3-trichloropropane).

It should be noted that the analyses associated with a regulatory determination process are distinct from the analyses needed to develop a National Primary Drinking Water Regulation (NPDWR). Thus, a decision to regulate is the beginning of the Agency's regulatory development process, not the end. For example, the EPA may find at a later point in the regulatory development process, and based on additional or new information, that a contaminant does not meet the three statutory criteria for finalizing a NPDWR.

B. Background on the CCL and Regulatory Determinations

1. Statutory Requirements for CCL and Regulatory Determinations

Section 1412(b)(1)(B)(i) of the SDWA requires the EPA to publish the CCL every five years after public notice and an opportunity to comment. The CCL is a list of contaminants which are not subject to any proposed or promulgated NPDWRs but are known or anticipated to occur in public water systems (PWSs) and may require regulation under the SDWA. SDWA section 1412(b)(1)(B)(ii) directs the EPA to determine, after public notice and an opportunity to comment, whether to regulate at least five contaminants from the CCL every five years. Under Section 1412(b)(1)(A) of SDWA, the EPA makes a determination to regulate a contaminant in drinking water if the Administrator determines that:

(a) The contaminant may have an adverse effect on the health of persons;

(b) the contaminant is known to occur or there is substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and

(c) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

If the EPA determines that these three statutory criteria are met and makes a final determination to regulate a contaminant (*i.e.,* a positive determination), the Agency must publish a proposed Maximum Contaminant Level Goal (MCLG) [1] and NPDWR [2] within 24 months. After the proposal, the Agency must publish a final MCLG and promulgate a final NPDWR (SDWA section 1412(b)(1)(E)) within 18 months.[3]

The development of the CCL, regulatory determinations, and any subsequent rulemaking should be viewed as a progression where each process builds upon the previous process, including the collection of data and analyses conducted. The Agency's improvements in developing CCLs 3 and 4 provided a foundation for RD 4 by enhancing the EPA's ability to identify contaminants of concern for drinking water. Sections III and IV in this document provide more detailed information about the approach and outcomes for RD 4 and the contaminant-specific regulatory determinations.

2. The First Contaminant Candidate List (CCL 1) and Regulatory Determination (RD 1)

The EPA published the final CCL 1, which contained 60 chemical and microbiological contaminants, in the **Federal Register** (FR) on March 2, 1998 (63 FR 10273; USEPA, 1998). The Agency published the final regulatory determinations for nine of the 60 CCL 1 contaminants in the FR on July 18, 2003. The Agency determined that NPDWRs were not necessary for nine contaminants: *Acanthamoeba,* aldrin, dieldrin, hexachlorobutadiene, manganese, metribuzin, naphthalene, sodium, and sulfate (68 FR 42898; USEPA, 2003a). The Agency posted information about *Acanthamoeba* [4] on the EPA's website and issued health advisories [5] (HAs) for manganese, sodium, and sulfate.

3. The Second Contaminant Candidate List (CCL 2) and Regulatory Determination (RD 2)

The Agency published the final CCL 2 in the FR on February 24, 2005 (70 FR 9071; USEPA, 2005a) and carried forward the 51 remaining chemical and microbial contaminants listed on CCL 1. The Agency published the final regulatory determinations for 11 of the 51 CCL 2 contaminants in the FR on July 30, 2008. The Agency determined that NPDWRs were not necessary for 11 contaminants: Boron, the dacthal mono- and di-acid degradates, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), 1,3-dichloropropene (Telone), 2,4-dinitrotoluene, 2,6-dinitrotoluene, s-ethyl dipropylthiocarbamate (EPTC), fonofos, terbacil, and 1,1,2,2-

[1] An MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety. MCLGs are non-enforceable health goals. (40 CFR 141.2; 42 U.S.C. 300g–1)

[2] An NPDWR is a legally enforceable standard that applies to public water systems. An NPDWR sets a legal limit (called a maximum contaminant level or MCL) or specifies a certain treatment technique (TT) for public water systems for a specific contaminant or group of contaminants. The MCL is the highest level of a contaminant that is allowed in drinking water and is set as close to the MCLG as feasible using the best available treatment technology and taking cost into consideration.

[3] The statute authorizes a nine-month extension of this promulgation date.

[4] Consumer information about *Acanthamoeba* for people who wear contact lenses can be found at *http://water.epa.gov/action/advisories/acanthamoeba/index.cfm.*

[5] Health advisories provide information on contaminants that can cause human health effects and are known or anticipated to occur in drinking water. The EPA's health advisories are non-enforceable and provide technical guidance to states agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. Health advisories can be found at *http://water.epa.gov/drink/standards/hascience.cfm.*

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tetrachloroethane (73 FR 44251; USEPA, 2008a). The Agency issued new or updated health advisories for boron, dacthal degradates, 2,4-dinitrotoluene, 2,6-dinitrotoluene, and 1,1,2,2-tetrachloroethane.

4. The Third Contaminant Candidate List (CCL 3) and Regulatory Determination (RD 3)

The Agency published the final CCL 3, which listed 116 contaminants, in the FR on October 8, 2009 (74 FR 51850; USEPA, 2009a). In developing CCL 3, the EPA improved and built upon the process that was used for CCL 1 and CCL 2. The CCL 3 process was based on substantial expert input and recommendations from the National Academy of Science's (NAS) National Research Council (NRC) and the National Drinking Water Advisory Council (NDWAC) as well as input from the public. Based on these consultations and input, the EPA developed a multi-step process to select candidates for the final CCL 3, which included the following key steps:

(a) Identification of a broad universe of ~7,500 potential drinking water contaminants (the CCL 3 Universe);

(b) screening the CCL 3 Universe to a preliminary CCL (PCCL) of ~600 contaminants based on the potential to occur in PWSs and the potential for public health concern; and

(c) evaluation of the PCCL contaminants based on a more detailed review of the occurrence and health effects data to identify a list of 116 CCL 3 contaminants.

The Agency published its preliminary regulatory determinations for contaminants listed on the CCL 3 in the FR on October 20, 2014 (79 FR 62715; USEPA, 2014a). In that document, the EPA made preliminary determinations for 5 of the 116 contaminants listed on the CCL 3 including a preliminary positive determination for strontium and preliminary negative determinations for dimethoate, 1,3-dinitrobenzene, terbufos, and terbufos sulfone. On January 4, 2016 (81 FR 13; USEPA, 2016a), the EPA finalized the negative determinations for dimethoate, 1,3-dinitrobenzene, terbufos, and terbufos sulfone. The EPA announced a delay in issuing a final regulatory determination on strontium in order to consider additional data. Additional discussion on strontium is provided in Section V of this document.

The EPA also published an off-cycle final determination to regulate one CCL 3 contaminant, perchlorate, on February 11, 2011 (76 FR 7762; USEPA, 2011a) during the RD 3 cycle (bringing the total number of final determinations to five). Additional information about the perchlorate determination can be found in that document.

5. The Fourth Contaminant Candidate List (CCL 4) and Regulatory Determination (RD 4)

The final CCL 4 was published on November 17, 2016 (81 FR 81099; USEPA, 2016b) and is the latest CCL published by EPA. The final CCL 4 consists of 97 chemicals or chemical groups and 12 microbiological contaminants. Most CCL 4 contaminants were carried over from CCL 3 (which, as described above, was developed according to a rigorous process with input from multiple stakeholders over the course of multiple years). The EPA added two contaminants (manganese and nonylphenol) to the CCL 4 list based on nominations. The EPA removed from the list those CCL 3 contaminants that had been subject to recent preliminary and/or final regulatory determinations (perchlorate, dimethoate, 1,3-dinitrobenzene, terbufos, terbufos sulfone, and strontium) and three pesticides with cancelled registrations (disulfoton, fenamiphos, and molinate).

III. Approach and Overall Outcomes for RD 4

This section describes (a) the approach the EPA used to identify and evaluate contaminants for the Agency's fourth round of Regulatory Determination (RD 4) along with the overall outcome of applying this approach, (b) the supporting RD 4 documentation, and (c) the technical analyses and sources of health and occurrence information.

A. Summary of the Approach and Overall Outcomes for RD 4

The approach taken under RD 4 is similar to that used in previous rounds of Regulatory Determination and formalized in a written Protocol under Regulatory Determination 3. The Regulatory Determination 4 Protocol, found in Appendix E of the Regulatory Determination 4 Support Document (USEPA, 2019a), like the Regulatory Determination 3 protocol, specifies a three-phase process. The three phases are: (1) The Data Availability Phase, (2) the Data Evaluation Phase, and (3) the Regulatory Determination Assessment Phase. Figure 1 provides an overview of the process the EPA uses to identify which CCL 4 contaminants are candidates for regulatory determinations and the SDWA statutory criteria considered in making the regulatory determinations. For more detailed information on the three phases of the RD 4 process please refer to the Regulatory Determination 4 Protocol (Appendix E to USEPA, 2019a).

SDWA 1412 (b)(1)(C) requires that the Administrator prioritize selection of contaminants that present the greatest public health concern. The Administrator, in making such selections, shall take into consideration, among other factors of public health concern, the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population. Because the RD 4 process includes consideration of human health effects, the Agency's Policy on Evaluating Health Risks to Children (USEPA, 1995a) to consistently and comprehensively address children's unique vulnerabilities, recently reaffirmed by Administrator Wheeler (USEPA, 2018a), applies to this action. We have explicitly considered children's health in the RD 4 process by reviewing all the available children's exposure and health effects information.

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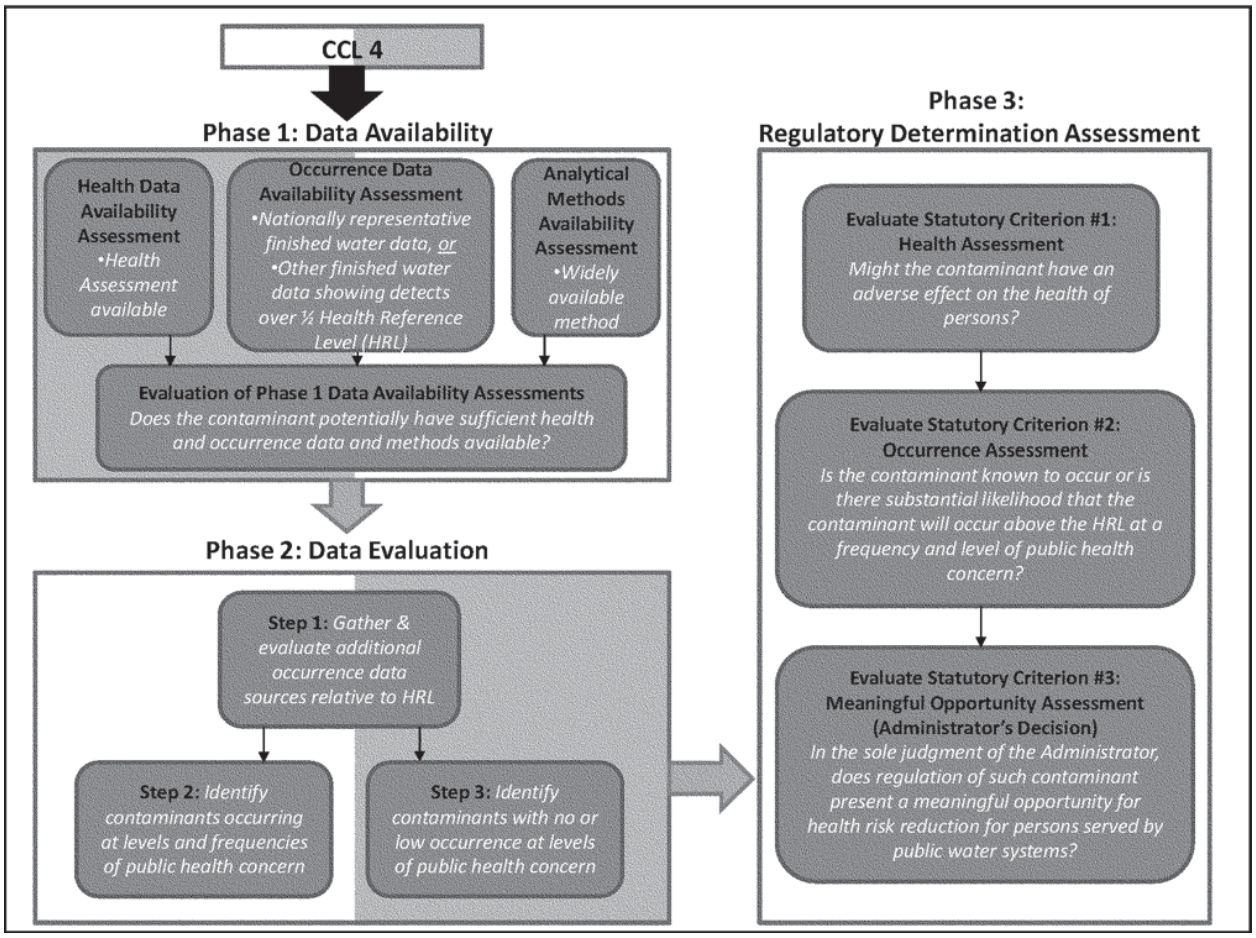
Figure 1: The Three Primary Phases of the RD 4 Process



1. Phase 1 (Data Availability Phase)

In Phase 1, the *Data Availability Phase,* the Agency identifies contaminants that have sufficient health and occurrence data to proceed to Phase 2 and be listed on a ''short list'' for further evaluation. SDWA 1412(b)(1)(B)(ii)(II) requires that the EPA consider the best available public health information in making the regulatory determination.

To identify contaminant health effects data that are sufficient to make a regulatory determination regarding potential adverse health effect(s), the Agency considers whether an EPA health assessment or an externally peer-reviewed health assessment from another Agency is available, from which a health reference level (HRL) [6] sufficient to inform a regulatory determination can be derived. (See Section III.C.1 of this document for information about how HRLs are derived.) Consistent with SDWA 1412.b.(3)(A)(i), EPA used health assessments to derive an HRL that the Agency has concluded are the best available peer reviewed science finalized before March 1, 2019. EPA establishes a cutoff date where it no longer considers new health-based information in order to allow for timely determinations and reviews. The EPA did not use draft health assessments to derive HRLs. Sources of health assessments may include: (a) EPA's Office of Water (OW) health assessments: Health Advisory (HA) Documents and Health Effects Support Documents (HESDs); (b) EPA's Office of Research and Development (ORD) Integrated Risk Information System (IRIS) assessments; (c) EPA's ORD Provisional Peer-Reviewed Toxicity Values (PPRTVs); (d) EPA's Office of Pesticide Programs (OPP) health assessments: Reregistration Eligibility Decisions (REDs), Interim Reregistration Eligibility Decisions (IREDs), Tolerance Reassessment Progress and Risk Management Decisions (TREDs), and Health Effects Division Human Health Risk Assessments (HED HHRAs); (e) U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles; (f) Health Canada Guidelines for Drinking Water; (g) the World Health Organization (WHO) Drinking Water Guidelines; and (h) publicly available state assessments that have been externally peer-reviewed and provide new science not considered in the other RD 4 assessment sources listed above. To support a regulatory determination, the EPA evaluates whether a health assessment used methods, standards, and guidelines comparable to those of current EPA guidelines and guidance documents. If a suitable health assessment is not available for a contaminant, the

[6] An HRL is a health-based concentration against which the Agency evaluates occurrence data when making decisions about preliminary regulatory determinations. An HRL is not a final determination on establishing a protective level of a contaminant in drinking water for a particular population; it is derived prior to development of a complete health and exposure assessment and can be considered a screening value.

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contaminant will not proceed to Phase 2. The EPA is aware of draft health assessments that have not yet been finalized for contaminants on which the EPA is making a preliminary determination today. Once finalized, the EPA will consider these new sources of information in future regulatory decision making.

To identify contaminant occurrence data that are sufficient to make a regulatory determination regarding the frequency and level of occurrence in PWSs, the Agency considers nationally representative finished water data (samples are collected after the water undergoes treatment). The following sources, administered or overseen by the EPA, include finished water occurrence data that are considered nationally representative: (a) The Third Unregulated Contaminant Monitoring Rule (UCMR 3); (b) the Second Unregulated Contaminant Monitoring Rule (UCMR 2); (c) the First Unregulated Contaminant Monitoring Rule (UCMR 1); (d) the Unregulated Contaminant Monitoring (UCM) program; and (e) the National Inorganics and Radionuclides Survey (NIRS).[7]

If nationally representative data are not available, the EPA identifies and evaluates other finished water data, which may include other national assessments, regional data, state, and more localized finished water assessments. These other finished water data may include assessments that are geographically distributed across the nation but not intended to be statistically representative of the nation. These other finished water data include: (a) Finished water assessments for Federal agencies (*e.g.,* EPA and the United States Geological Survey (USGS));[8] (b) state-level finished water monitoring data; (c) research performed by institutions, universities, and government scientists (information published in the scientific literature); and/or (d) other supplemental finished water monitoring surveys (*e.g.,* Pesticide Monitoring Program (PMP), and other targeted surveys or localized state/federal monitoring surveys).

The EPA prefers to have nationally representative data when making regulatory determinations but may also use other sources of finished water data to address the occurrence-related aspects of the statutory criteria when deciding to regulate a contaminant. In Phase 1, the Agency does this by assessing whether the non-nationally-representative finished water occurrence data show at least one detection in finished water at levels >½ the HRL[9] for the critical endpoint. If a contaminant has nationally representative or non-nationally representative finished water occurrence data showing at least one detection >½ HRL, the contaminant passes the Occurrence Data Availability Assessment and proceeds to the next phase of analysis. However, it is difficult to determine that a contaminant is not occurring or not likely to occur based on sources of non-nationally representative finished water occurrence data because the data are limited in scope and the contaminant could be occurring in other parts of the country that were not monitored.

In certain limited cases, a contaminant's occurrence data may have been gathered using a specialized or experimental method that is not in general use. If a widely available analytical method does not exist, the contaminant will not be a viable candidate for regulation with a Maximum Contaminant Level (MCL). With that in mind, in the Analytical Methods Availability Assessment, the EPA determines for each contaminant whether a widely available analytical method for monitoring exists. (A widely available analytical method is a method employing technology that is commonly in use at numerous drinking water laboratories.) If a widely available analytical method exists, the contaminant passes the Analytical Methods Availability Assessment. If a widely available analytical method does not exist, the EPA may advance the contaminant to Phase 2 if the Agency determines that indicator or surrogate monitoring, or use of a treatment technique (TT), could allow for effective regulation and there is compelling evidence of occurrence.

In addition to considering contaminants individually, the EPA also may consider issuing a regulatory determination for groups of contaminants. The EPA has regulated certain contaminants in drinking water collectively.

After conducting the health and occurrence data availability assessments, the Agency identifies those contaminants and contaminant groups that meet the following Phase 1 data availability criteria:

(a) An EPA health assessment or an externally peer-reviewed health assessment from another Agency that conforms with the current EPA guidelines is available, from which an HRL can be derived;

(b) Either nationally representative finished water occurrence data are available, or other finished water occurrence data show occurrence at levels >½ the HRL; and

(c) A widely available analytical method for monitoring is available.

If a contaminant or group meets these three criteria, it is placed on a ''short list'' and proceeds to Phase 2. After evaluating the 109 CCL 4 contaminants and two additional contaminants (4-androstene-3,17-dione and testosterone)[10] in Phase 1, the Agency identified 25 CCL 4 contaminants to evaluate further in Phase 2 (contaminants listed in Table 1).

TABLE 1—CONTAMINANTS PROCEEDING FROM PHASE 1 TO PHASE 2

1,1,1,2-Tetrachloroethane.
1,1-Dichloroethane.
1,2,3-Trichloropropane.
1,4-Dioxane.
Acephate.
Acetochlor.
alpha-Hexachlorocyclohexane.
Aniline.
Chlorate.
Cobalt.
Cyanotoxins.
Legionella pneumophila.
Manganese.
Methyl bromide (Bromomethane).
Metolachlor.
Molybdenum.
Nitrobenzene.
N-Nitrosodiethylamine (NDEA).
N-Nitrosodimethylamine (NDMA).
N-Nitroso-di-n-propylamine (NDPA).
N-Nitrosopyrrolidine (NPYR).
Perfluorooctanesulfonic acid (PFOS).
Perfluorooctanoic acid (PFOA).
RDX.
Vanadium.

The remaining 84 CCL 4 contaminants and two additional contaminants (4-androstene-3,17-dione and testosterone) (listed in Table 2) did not meet one or more of the Phase 1 data availability criteria above and were not considered further for RD 4.

[7] Specific types of UCMR monitoring (*e.g.,* assessment monitoring and sometimes the screening survey) are considered nationally representative. These are described further in Section III.C.2.a.1 of this document.

[8] These may be assessments that are geographically distributed across the nation but not intended to be statistically representative of the nation. Examples include the EPA's 1996 Monitoring Requirements for Public Drinking Water Supplies, also known as the Information Collection Rule (USEPA, 1996), and various USGS water quality surveys.

[9] Note that the ½ HRL threshold is based on a recommendation from the NDWAC working group that provided recommendations on the first regulatory determination effort (USEPA, 2000).

[10] Contaminants monitored under UCMR 3 but not included in CCL 3 or CCL 4.

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TABLE 2—CONTAMINANTS NOT PROCEEDING FROM PHASE 1 TO PHASE 2

Has nationally representative finished water data but no health assessment

1,3-Butadiene.
3-Hydroxycarbofuran.
4-Androstene-3,17-dione.
Acetochlor ethanesulfonic acid (ESA).
Acetochlor oxanilic acid (OA).
Alachlor ESA.
Alachlor OA.
Chloromethane (Methyl chloride).
Equilin.
Estradiol (17-beta estradiol).
Estriol.
Estrone.
Ethinyl Estradiol (17-alpha ethynyl estradiol).
Germanium.
Halon 1011 (bromochloromethane).
HCFC–22.
Methyl tert-butyl ether.
Metolachlor ESA.
Metolachlor OA.
n-Propylbenzene.
sec-Butylbenzene.
Tellurium.
Testosterone.

Has available or in process health assessment and other finished drinking water data but no occurrence at levels >½ HRL

1-Butanol.
Acrolein.
Bensulide.
Benzyl chloride.
Captan.
Dicrotophos.
Diuron.
Ethoprop.
Ethylene glycol.
Ethylene thiourea (Maneb 12427382).
Formaldehyde.
Methamidophos.
Methanol.
N-Nitrosodiphenylamine (NDPhA) *.
Oxydemeton-methyl.
Oxyfluorfen.
Permethrin.
Profenofos.
Tebuconazole.
Tribufos.
Vinclozolin.
Ziram.

Has other finished drinking water data but no health assessment

17alpha-estradiol.
Acetaldehyde.
Adenovirus *.
Butylated hydroxyanisole.
Caliciviruses *.
Enterovirus *.
Equilenin.
Erythromycin.
Hexane.
Mestranol.
Mycobacterium avium *.
Naegleria fowleri *.
Nonylphenol.
Norethindrone (19-Norethisterone).

TABLE 2—CONTAMINANTS NOT PROCEEDING FROM PHASE 1 TO PHASE 2—Continued

Does not have nationally representative or other finished water data

2-Methoxyethanol.
2-Propen-1-ol.
4,4′-Methylenedianiline.
Acetamide.
Campylobacter jejuni.
Clethodim.
Cumene hydroperoxide.
Dimethipin.
Escherichia coli (O157).
Ethylene oxide.
Helicobacter pylori.
Hepatitis A virus.
Hydrazine.
Nitroglycerin.
N-Methyl-2-pyrrolidone.
o-Toluidine.
Oxirane, methyl-.
Quinoline.
Salmonella enterica.
Shigella sonnei.
Tebufenozide.
Thiodicarb.
Thiophanate-methyl.
Toluene diisocyanate.
Triethylamine.
Triphenyltin hydroxide (TPTH).
Urethane.

* Does not have a widely available analytical method for occurrence monitoring.

2. Phase 2 (Data Evaluation Phase)

In Phase 2, the Agency collects additional data on occurrence (including finished water data; ambient water data; data on use, production, and release; and information on environmental fate and transport), and more thoroughly evaluates this information (based on factors below) to identify contaminants that should proceed to Phase 3.

In Phase 2, the Agency focuses its efforts to identify those contaminants or contaminant groups that are occurring or have substantial likelihood to occur at levels and frequencies of public health concern. As noted in Section III.A, SDWA 1412.b.1.C requires that the Administrator select contaminants that present the greatest public health concern. To identify such contaminants, the Agency considers the following information:

(a) How many samples (number and percentage) have detections > HRL and ½ HRL in the nationally representative and other finished water occurrence data?

(b) How many systems (number and percentage) have detections > HRL and ½ HRL in the nationally representative and other finished water occurrence data?

(c) Are there uncertainties or limitations with the data and/or analyses, such as the age of the dataset, the detection limit level (*i.e.,* minimum reporting level [MRL[11]] > HRL), and/or representativeness of the data (*e.g.,* limited to a specific region) that may cause misestimation of occurrence in finished water at levels and frequency of public health concern?

After identifying contaminants that are occurring at levels and frequencies of public health concern to proceed to Phase 3, the Agency evaluates the remaining contaminants on the ''short list'' to determine which contaminants have no or low occurrence at levels of health concern that should proceed to Phase 3 for a potential negative determination. Because the primary goal of RD 4 is to focus on contaminants of public health concern, potential negative determinations are a lower priority than potential positive determinations. The Agency considers the following information in selecting contaminants of no or low potential for public health concern to proceed to Phase 3:

(a) Does the contaminant have nationally representative finished water data showing no or low number or percent of detections > HRL?

(b) If a contaminant has other finished water data in addition to nationally representative finished water data, does it support no or low potential for occurrence in drinking water? [12]

(c) Does additional occurrence information of high quality support the conclusion that there is low or no occurrence or potential for occurrence in drinking water? For example, is the occurrence in ambient/source water at levels below the HRL? How are releases to the environment or use/production changing over time?

(d) Are critical gaps in health and occurrence information/data minimal?

After evaluating the ''short list'' contaminants (listed in Table 1), the Agency identified 10 CCL 4 contaminants to proceed to Phase 3 (listed in Table 3). The contaminants are within one of the following Phase 2 data evaluation categories:

(a) A contaminant or part of a contaminant group occurring or likely to

[11] The MRL is the minimum concentration that is required to be reported quantitatively in a study. The MRL is set at a value that takes into account typical laboratory capabilities to reliably and cost-effectively detect and quantify a compound.

[12] Note that other finished water data (*i.e.,* non-nationally-representative occurrence data) tend to be limited in scope and the EPA does not use these data alone to support a determination that the contaminant is not or is not substantially likely to ''occur in PWSs with a frequency and at levels of public health concern,'' which would therefore be a decision ''not to regulate'' (*i.e.,* negative determination).

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occur at levels and frequencies of public health concern, or

(b) A contaminant not occurring or not likely to occur at levels and frequencies of public health concern and no data gaps.

TABLE 3—CONTAMINANTS PROCEEDING FROM PHASE 2 TO PHASE 3

1,1-Dichloroethane.
1,4-Dioxane.
1,2,3-Trichloropropane.
Acetochlor.
Methyl Bromide.
Metolachlor.
Nitrobenzene.
PFOA.
PFOS.
RDX.

Note that the Agency does not have a threshold for occurrence in drinking water that triggers whether a contaminant is of public health concern. A determination of public health concern requires a consideration of a number of factors, some of which include the health effect(s), the potency of the contaminant, the level at which the contaminant is found in drinking water, the frequency at which the contaminant is found, the geographic distribution (national, regional, or local occurrence), other possible sources of exposure, and potential impacts on sensitive populations or lifestages. Given the many possible combinations of factors, a simple threshold is not viable. In the end, a determination of whether there is a meaningful opportunity for health risk reduction by regulation of a contaminant in drinking water is a highly contaminant-specific decision that takes into consideration multiple factors.

The remaining 15 CCL 4 contaminants (listed in Table 4) did not proceed to Phase 3 and were not considered for RD 4 because of one or more of the following critical health, occurrence, and/or other data gaps:

(a) An updated health assessment completed by March 1, 2019 was not identified;

(b) Critical health effects gap (*e.g.,* lack of data to support quantification for the oral route of exposure);

(c) Lack of nationally representative finished water occurrence data and lack of sufficient other data to demonstrate occurrence at levels and frequencies of public health concern; and

(d) Critical occurrence data limitation or gap (*e.g.,* inconsistent results and/or trends in occurrence data requiring further research; significant uncertainty in occurrence analyses and/or data).

Table 4 identifies the health, occurrence, and/or other data gaps that prevented the following 15 contaminants from moving forward for RD 4. The Agency continues to conduct research and collect information to fill the data and information gaps identified in Table 4.

TABLE 4—DATA AND RATIONALE SUMMARY OF THE 15 CONTAMINANTS IN PHASE 2 NOT PROCEEDING TO PHASE 3

Number	Contaminant	Health data available	Occurrence data available	Rationale
1	1,1,1,2-Tetrachloroethane	Yes	Yes	Health data gap (a review of the current literature is needed to decide if an update to the 1987 IRIS health assessment is warranted).
2	Acephate	Yes	No	Occurrence data gaps (no nationally representative finished water data or sufficient other finished water data).
3	alpha-Hexachlorocyclohexane	Yes	No	Occurrence data gaps (no nationally representative finished water data or sufficient other finished water data).
4	Aniline	Yes	No	Occurrence data gaps (no nationally representative finished water data or sufficient other finished water data).
5	Chlorate			Will be evaluated and considered as part of the review of the existing Disinfectants/Disinfection Byproducts (D/DBP) rules.[13 14]
6	Cobalt	Yes	Yes	Health data gap (updated health assessment needed to consider new subchronic and developmental studies).
7	Cyanotoxins	Yes	No	Health advisories available for some specific cyanotoxins (microcystins and cylindrospermopsin); occurrence data gaps (insufficient nationally representative finished water data or other finished water data). Certain cyanotoxins are being monitored under UCMR 4 but final UCMR 4 data will not be complete in time for preliminary determination.
8	*Legionella pneumophila*	Yes	No	MCLG available; occurrence data gaps (no nationally representative finished water data or sufficient other finished water data). Will be evaluated and considered as part of the review of the existing SWTR.[14]
9	Manganese	No	No	Health and occurrence data gaps (updated health assessment[15] not completed by RD 4 cutoff date). Manganese is being monitored for under UCMR 4 but final UCMR 4 data will not be complete in time for preliminary determination.
10	Molybdenum	No	Yes	Health data gap (updated assessment needed to consider multiple new studies).
11	N-Nitrosodiethylamine (NDEA)			Will be evaluated and considered as part of the review of the existing D/DBP rules.[13]
12	N-Nitrosodimethylamine (NDMA)			Will be evaluated and considered as part of the review of the existing D/DBP rules.[13]
13	N-Nitroso-di-n-propylamine (NDPA).			Will be evaluated and considered as part of the review of the existing D/DBP rules.[13]
14	N-Nitrosopyrrolidine (NPYR)			Will be evaluated and considered as part of the review of the existing D/DBP rules.[13]

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TABLE 4—DATA AND RATIONALE SUMMARY OF THE 15 CONTAMINANTS IN PHASE 2 NOT PROCEEDING TO PHASE 3—Continued

Number	Contaminant	Health data available	Occurrence data available	Rationale
15	Vanadium	Yes	Yes	Health data gap; undergoing assessment by EPA IRIS: *https://www.epa.gov/sites/production/files/2019-04/documents/iris_program_outlook_apr2019.pdf.*

3. Phase 3 (Regulatory Determination Assessment Phase)

Phase 3, the Regulatory Determination Assessment Phase, involves a complete evaluation of the statutory criteria for each contaminant or group of contaminants that proceed from Phase 2 and have sufficient information and data for making a regulatory determination. In this phase, the Agency evaluates the following statutory criteria (SDWA 1412(b)(1)(A)):

(a) Statutory Criterion #1—The contaminant may have an adverse effect on the health of persons. To evaluate criterion #1, the EPA evaluates whether a contaminant has an EPA health assessment, or an externally peer-reviewed health assessment from another Agency that is publicly available and conforms with current the EPA guidelines, from which an HRL can be derived. The HRL derived in or from the health assessment takes into account the MOA, the critical health effect(s), the dose-response relationship for critical health effect(s), and impacts on sensitive population(s) or lifestages. HRLs are preliminary health-based concentrations against which occurrence data is evaluated to determine if contaminants may occur at levels of potential public health concern. HRLs are not final determinations on establishing a protective level of a contaminant in drinking water for any particular population. HRLs are derived prior to the development of a complete health and exposure assessment and can be considered screening-level values.

If an acceptable health assessment that demonstrates adverse health effects is available, the Agency answers ''yes'' to the first statutory criterion. Otherwise, the Agency answers ''no'' to the first statutory criterion. (In practice, it is expected that any contaminant that reaches Phase 3 would receive a ''yes'' to the first criterion.)

(b) Statutory Criterion #2—The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern. The EPA compares the occurrence data for each contaminant to the HRL to determine if the contaminant occurs at a frequency and levels of public health concern. The types of occurrence data used at this stage are described in section III.C.2, Evaluation of Contaminant Occurrence and Exposure. The Agency may consider the following factors when identifying contaminants or contaminant groups that are occurring at frequencies and levels of public health concern:

- How many samples (number and percentage) have detections > HRL in the nationally representative and other finished water occurrence data?
- How many systems (number and percentage) have detections > HRL in the nationally representative and other finished water occurrence data?
- Is the geographic distribution of the contaminant occurrence national, regional, or localized?
- In addition to the number of systems, what type of systems does the contaminant occur in? Does the contaminant occur in large or small systems? Does the contaminant occur in surface or groundwater systems?
- Are there significant uncertainties or limitations with the data and/or analyses, such as the age of the dataset, the detection limit level (*i.e.,* MRL > HRL), and/or representativeness of the data (*e.g.,* limited in scope to a specific region)?

Additional, less important factors that the Agency considers when identifying contaminants or contaminant groups that are occurring at frequencies and levels of public health concern also include:

- How many samples (number and percentage) have detections > ½ HRL in the nationally representative and other finished water occurrence data?
- How many systems (number and percentage) have detections > ½ HRL in the nationally representative and other finished water occurrence data?
- How many samples (number and percentage) have detections > HRL and ½ HRL in the ambient/source water occurrence data?
- How many monitoring sites (number and percentage) have detections > HRL and ½ HRL in the ambient/source water occurrence data?
- Are production and use trends for the contaminant increasing or decreasing?
- How many pounds are discharged annually to surface water and/or released to the environment?
- Do the environmental fate and transport parameters indicate that the contaminant would persist and/or be mobile in water?
- Is the contaminant introduced by water treatment processes that provide public health benefits such that it is relevant to risk-balancing considerations?
- Are there additional uncertainties or limitations with the data and/or analyses that should be considered?

If a contaminant is known to occur or substantially likely to occur at a frequency and level of health concern in public water systems based on consideration of the factors listed above, then the Agency answers ''yes'' to the second statutory criterion.

(c) Statutory Criterion #3—In the sole judgment of the Administrator, regulation of the contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems. The EPA evaluates the population exposed at the health level of concern along with several other

[13] Under RD 3 (79 FR 62716), the EPA noted that disinfection byproducts (DBPs) need to be evaluated collectively, because the potential exists that the treatment used to control a specific DBP could affect the concentrations of other DBPs and potentially microorganisms.

[14] Under the Six-Year Review 3 (82 FR 3518, USEPA, 2016c), the Agency completed a detailed review of 76 NPDWRs and determined that eight NPDWRs were candidates for regulatory revision. The eight NPDWRs are included in the Stage 1 and the Stage 2 Disinfectants and Disinfection Byproducts Rules, the Surface Water Treatment Rule (SWTR), the Interim Enhanced Surface Water Treatment Rule, and the Long Term 1 Enhanced Surface Water Treatment Rule.

[15] Health Canada finalized their Manganese Guideline for Canadian Drinking Water Quality in June 2019. The Guideline summarizes new health effects information published since the EPA's manganese health assessment in 2004 (*https://www.canada.ca/content/dam/hc-sc/documents/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-manganese/pub-manganese-0212-2019-eng.pdf*).

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factors to determine if regulation presents a meaningful opportunity for health risk reduction. Among other things, the EPA may consider the following factors in evaluating statutory criterion #3:

- What is the nature of the health effect(s) identified in statutory criterion #1?
- Are there sensitive populations that may be affected (evaluated either qualitatively or quantitatively [16])?
- Based on the occurrence information for statutory criterion #2, including the number of systems potentially affected, what is the national population exposed or served by systems with levels > HRL and ½ HRL?
- For non-carcinogens, are there other sources of exposure that should be considered (*i.e.,* what is the relative source contribution (RSC) from drinking water)?
- What is the geographic distribution of occurrence (*e.g.,* local, regional, national)?
- Are there any uncertainties and/or limitations in the health and occurrence information or analyses that should be considered?
- Are there any limiting considerations related to technology (*e.g.,* lack of available treatment or analytical methods [17])?

If the Administrator, in his or her sole judgement, determines that there is a meaningful opportunity to reduce risk by regulating the contaminant in drinking water, then the Agency answers ''yes'' to the third statutory criterion.

If the Agency answers ''yes'' to all three statutory criteria in Phase 3 for a particular contaminant, then the Agency makes a positive preliminary determination. Additionally, after identifying compounds occurring at frequencies and levels of public health concern, if any, the Agency may initiate a systematic literature review to identify new studies that may influence the derivation of a Reference Dose (RfD) and/or Cancer Slope Factor (CSF). The list of potentially relevant health effect studies that could affect the derivation of an RfD or CSF identified through the systematic review process would then be placed in the docket at the time of the Preliminary Determination for public comment (discussed further in Section IV of this document).

If, after considering input provided during the public comment period, the Agency again answers ''yes'' to all three statutory criteria, the Agency then makes a positive final determination that regulation is necessary and proceeds to develop an MCLG and NPDWR. The Agency has 24 months to publish a proposed MCLG and NPDWR and an additional 18 months to publish a final MCLG and promulgate a final NPDWR.[18] It should be noted that the analyses associated with a regulatory determination process are distinct from the more detailed analyses needed to develop an NPDWR. Thus, a decision to regulate is the beginning of the Agency's regulatory development process, not the end. For example, the EPA may find at a later point in the regulatory development process, and based on additional or new information, that the contaminant no longer meets the three statutory criteria and may, as a result, withdraw the determination to regulate.

If a contaminant has sufficient information and the Agency answers ''no'' to any of the three statutory criteria, based on the available data, then the Agency considers making a negative determination that an NPDWR is not necessary for that contaminant at that time. A final determination not to regulate a contaminant is, by statute, a final Agency action and is subject to judicial review. If a negative determination or no determination is made for a contaminant, the Agency may decide to develop a HA, which provides non-regulatory concentration values for drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (*e.g.,* one-day, ten-days, several years, and a lifetime). The EPA's HAs are non-enforceable and non-regulatory and provide technical information to states agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination.

While a negative determination is considered a final Agency action under SDWA for a round of regulatory determinations, the contaminant may be relisted on a future CCL based on newly available health and/or occurrence information.

At this time, the Agency is not making preliminary regulatory determinations for two of the ten contaminants that proceeded to Phase 3. After evaluating the remaining CCL 4 contaminants in Table 3 against the three SDWA criteria and considering the factors listed for each, the Agency is making a preliminary regulatory determination for these eight CCL 4 contaminants. Table 5 provides a summary of the 10 contaminants evaluated for Phase 3 and the preliminary regulatory determination outcome for each. The Agency seeks comment on the preliminary determination to regulate two contaminants (PFOS and PFOA) and to not regulate six contaminants (1,1-dichloroethane, acetochlor, methyl bromide, metolachlor, nitrobenzene, and RDX). Section IV.B of this document provides a more detailed summary of the information and the rationale used by the Agency to reach its preliminary decisions for these contaminants. Section V of this document provides more information about 1,4-dioxane and 1,2,3-trichloropropane, the two Phase 3 contaminants for which the EPA is not making a preliminary regulatory determination at this time.

TABLE 5—CONTAMINANTS EVALUATED IN PHASE 3 AND THE REGULATORY DETERMINATION OUTCOME

Number	RD 3 contaminants	Preliminary determination outcome
1	1,1-Dichloroethane	Do Not Regulate.
2	1,4-Dioxane	No Determination.
3	1,2,3-Trichloropropane.	No Determination.
4	Acetochlor	Do Not Regulate.
5	Methyl Bromide	Do Not Regulate.
6	Metolachlor	Do Not Regulate.
7	Nitrobenzene	Do Not Regulate.
8	PFOA	Regulate.
9	PFOS	Regulate.
10	RDX	Do Not Regulate.

B. Supporting Documentation for EPA's Preliminary Determination

For this action, the EPA prepared several supporting documents that are available for review and comment in the EPA Water Docket. These support documents include:

[16] If appropriate and available, the Agency quantitatively takes into account exposure data applicable to sensitive populations or lifestages when deriving HRLs for regulatory determinations. When data are not available on sensitive populations, the derivation of the RfD typically includes an uncertainty factor to account for the weakness in the database. Additionally, the EPA will use exposure factors relevant to the sensitive population in deriving the HRL. See section III.C.1. Sensitive populations are also qualitatively considered by providing national prevalence estimates for a particular sensitive population, if available.

[17] If the Agency decides to regulate a contaminant, the SDWA requires that the EPA issue a proposed regulation within two years of the final determination. As part of the proposal, the Agency must list best available technologies (BATs), small system compliance technologies (SSCTs), and approved analytical methods if it proposes an enforceable MCL. Alternatively, if the EPA proposes a TT instead of an MCL, the Agency must identify the TT. The EPA must also prepare a health risk reduction and cost analysis. This analysis includes an extensive evaluation of the treatment costs and monitoring costs at a system level and aggregated at the national level. To date, treatment information and approved analytical methods have not been significant factors in regulatory determinations but are important considerations for regulation development.

[18] The statute authorizes a nine-month extension of this promulgation date.

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• The comprehensive regulatory support document, *Regulatory Determination 4 Support Document* (USEPA, 2019a), summarizes the information and data on the physical and chemical properties, uses and environmental release, environmental fate, potential health effects, occurrence and exposure estimates, analytical methods, treatment technologies, and preliminary determinations. Additionally, Appendix E of the Regulatory Determinations 4 Support Document describes the approach implemented by the Agency to evaluate the CCL 4 contaminants in a three-phase process and select the contaminants for preliminary determinations for RD 4.

• A comprehensive technical occurrence support document for UCMR 3, *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b). This occurrence support document includes more detailed information about UCMR 3, how the EPA assessed the data quality, completeness, and representativeness, and how the data were used to generate estimates of drinking water contaminant occurrence in support of these regulatory determinations.

C. Analyses Used To Support the Preliminary Regulatory Determinations

Sections III.C.1 and 2 of this action outline the health effects and occurrence/exposure evaluation process the EPA used to support these preliminary determinations.

1. Evaluation of Adverse Health Effects

This section describes the approach for deriving the HRL for the contaminants under consideration for regulatory determinations. HRLs are health-based drinking water concentrations against which the EPA evaluates occurrence data to determine if contaminants occur at levels of potential public health concern. HRLs are not final determinations on establishing a protective level of a contaminant in drinking water for any particular population and are derived prior to the development of a complete health and exposure assessment. More specific information about the potential for adverse health effects for each contaminant is presented in section IV.B of this action.

a. Derivation of an HRL

There are two general approaches to the derivation of an HRL. One general approach is used for chemicals with a threshold dose-response (usually involving non-cancer endpoints, and occasionally cancer endpoints). The second general approach is used for chemicals that exhibit a linear, non-threshold response to dose (as is typical of carcinogens). A variant of the second approach is used when a carcinogen with a linear dose-response has a known mutagenic MOA (USEPA, 2019a).

HRLs for contaminants with a threshold dose-response (typically non-cancer endpoints) are calculated as follows:

$$HRL = RfD * \frac{BW}{DWI} * RSC$$

HRLs for contaminants with a linear dose-response (typically cancer endpoints) are calculated as follows:

$$HRL = \frac{CRL}{CSF} * \frac{BW}{DWI}$$

HRLs for carcinogenic contaminants with a known mutagenic MOA are calculated as follows:

$$HRL = \frac{CRL}{CSF} * \frac{1}{\sum_i \left(\frac{DWI_i}{BW_i} * f_i * ADAF_i\right)}$$

Where:

HRL = Health Reference Level (μg/L)
RfD = Reference Dose (mg/kg/day)
DWI = Drinking Water Intake (L)
BW = Body weight (kg)
CSF = Cancer Slope Factor $(mg/kg/day)^{-1}$
CRL = Cancer risk level, assumed to be 1 in a million (1×10^{-6})
ADAF = The Age Dependent Adjustment Factor for the age group *i* (by default, ADAF = 10 from birth to two years of age; ADAF = 3 from two to sixteen years of age; ADAF = 1 from sixteen to seventy years of age)
f = fraction of applicable period of exposure (by default, lifetime of seventy years) represented by age group *i*
RSC = Relative Source Contribution, which is the portion (percentage) of an individual's exposure attributed to drinking water rather than other sources (*e.g.,* food, ambient air). In Regulatory Determination, a 20% RSC is used for HRL derivation because (1) HRLs are developed prior to a complete exposure assessment, and (2) 20% is the lowest and most conservative RSC used in the derivation of an MCLG for drinking water.

b. Protection of Sensitive Subpopulations

In prioritizing the contaminants of greatest public health concern for regulatory determination, Section 1412(b)(1)(C) of SDWA requires the Agency to consider ''among other factors of public health concern, the effect of such contaminants upon subgroups that comprise a meaningful portion of the general population (such as infants, children, pregnant women, the elderly, individuals with a history of serious illness, or other subpopulations) that are identifiable as being at greater risk of adverse health effects due to exposure to contaminants in drinking water compared to the general population.'' If appropriate and if adequate data are available, the Agency will use data from sensitive populations and lifestages quantitatively when deriving HRLs for regulatory determinations in the following manner:

(a) For non-carcinogens, an HRL can be developed for a sensitive population if data are available to associate exposure with the critical health endpoint in a specific group or during a specific period of sensitivity. Age-specific drinking water intake (DWI) to body weight (BW) ratio values from the *Exposure Factors Handbook* (USEPA, 2011b) can be used to reflect the period of exposure more accurately. The Agency can also apply specific uncertainty factors (UFs) when deriving the RfD if toxicological data are lacking for a sensitive population. Two common justifications for UFs that can be applied to account for sensitive populations are: (1) Variation in sensitivity among the members of the human population (*i.e.,* intraspecies variability) and (2) uncertainty associated with an incomplete database.

(b) For HRLs developed for carcinogens with a mutagenic MOA, the 2005 Cancer Guidelines require consideration of increased risks due to early-life exposure. When chemical-specific data to quantify the increased risk are lacking, Age Dependent Adjustment Factors (ADAFs) are applied, generally with a 10-fold adjustment for early life exposures, a 3-fold adjustment for childhood/adolescent exposures, and no additional adjustment for exposures later in life (as shown above). Age-specific drinking-water-intake-to-body-weight ratio values are also applied from the *Exposure Factors Handbook* (USEPA, 2011b). In cases where the data on the MOA are lacking, the default low-dose linear extrapolation approach without ADAFs is used.

While this action is not subject to Executive Order 13045: Protection of Children from Environmental Health and Safety Risks, the Agency's Policy on Evaluating Health Risks to Children (USEPA, 1995a), recently reaffirmed by Administrator Wheeler (USEPA, 2018a), was still applied for the RD 4 preliminary determination. The EPA's policy (USEPA, 1995a) requires the EPA to consistently and comprehensively address children's unique vulnerabilities. For example, if exposure to a contaminant considered for RD 4 was associated with a developmental

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effect, the EPA derived HRLs using the exposure factors for a bottle-fed infant to be protective of children, assuming that the adverse effect identified could occur during the window of time when the infant is formula-fed (see metolachlor in Section IV.B as an example).

c. Sources of Data/Information for Health Effects

The EPA relies on health assessments produced by the Agency itself and produced by other agencies. The criteria for accepting a health assessment for RD 4 are described in Section III.A.1, above. Table 6 summarizes the sources of the health assessment data for each chemical with a preliminary determination under RD 4. As noted in Section III.A.3, in the case of potential positive determinations, the EPA searches for and evaluates additional data and information from the published literature to supplement the health assessment (Note that the two Phase 3 contaminants that are not receiving a preliminary determination are not discussed here. They are 1,4-dioxane and 1,2,3-trichloropropane. See section V of this document for more on those two contaminants.)

Table 6. Sources of Data/Information for Health Effects

Chemical	EPA IRIS	EPA OW Assessment	EPA OPP Human Health Risk Assessment (HHRA)	EPA ORD Provisional Peer-Reviewed Toxicity Value (PPRTV)	Agency for Toxic Substances and Disease Registry (ATSDR)	California EPA	Health Canada	World Health Organization (WHO)
1 1,1-Dichloroethane	1990			2006	2015	2003		2003
2 Acetochlor	1993		2018					
3 Methyl Bromide (Bromomethane)	1988	1989	2006	2007	1992			
4 Metolachlor	1990	1988	2018				1990	2003
5 Nitrobenzene	2009				1990			2009
6 RDX	2018	1992			2012			
7 PFOA		2016				2019	2018	
8 PFOS		2016				2019	2018	

2. Evaluation of Contaminant Occurrence and Exposure

The EPA uses data from many sources to evaluate occurrence and exposure from drinking water contaminants. The following comprise the primary sources of finished drinking water occurrence data discussed in this **Federal Register** document:

- Unregulated Contaminant Monitoring Rules (UCMR 1, 2, and 3)
- UCM Program Rounds 1 and 2, and
- Data collected by states.

Several of the primary sources of finished water occurrence data are designed to be statistically representative of the nation. These data sources include UCMR 1, UCMR 2, and UCMR 3.

The Agency also evaluates supplemental sources of information on occurrence in drinking water, occurrence in ambient and source water, and information on contaminant production and release to augment and complement these primary sources of drinking water occurrence data. Section III.C.2.a. of this action provides a brief summary of the primary sources of finished water occurrence data, and sections III.C.2.b and II.C.2.c provide brief summary descriptions of some of the supplemental sources of occurrence information and/or data. These descriptions do not cover all the sources that the EPA reviews and evaluates. For individual contaminants, the EPA reviews additional published reports and peer-reviewed studies that may provide the results of monitoring efforts in limited geographic areas. A summary of the occurrence data and the results or findings for each of the contaminants considered for regulatory determination is presented in section IV.B, the contaminant profiles section, and the data are described in further detail in the *Regulatory Determination 4 Support Document* (see USEPA, 2019a).

a. Primary Sources of Finished Drinking Water Occurrence Data

The following sections provide a brief summary of the finished water occurrence data sources used in RD 4. Table 8 in section IV lists the primary data source/finding used to evaluate each of the eight contaminants considered for regulatory

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determinations. Section V of this document provides more information about 1,4-dioxane and 1,2,3-trichloropropane, the two Phase 3 contaminants for which the EPA is not making a preliminary regulatory determination at this time. The contaminant-specific discussions in section IV provide more detailed information about the primary data source findings as well as any supplemental occurrence information.

(1) The Unregulated Contaminant Monitoring Rules (UCMR 1, UCMR 2, and UCMR 3)

The UCMR is the EPA's primary vehicle for collecting monitoring data on the occurrence of unregulated contaminants in PWSs. SDWA section 1412(b)(1)(B)(ii)(II) requires that the EPA include consideration of the data produced by the UCMR program in making regulatory determinations. The UCMR list is published every five years and is designed to collect nationally representative occurrence data that is developed in coordination with the CCL and Regulatory Determination processes. The UCMR sampling is limited by statute to no more than 30 contaminants every five years (SDWA section 1445(a)(2)). PWSs and state primacy agencies are required to report the data to the EPA. The EPA published the lists and requirements for the UCMR 1 on September 17, 1999 (64 FR 50556, September 17, 1999, USEPA, 1999), and the monitoring was conducted primarily during 2001–2003. UCMR 2 was published on January 4, 2007 (72 FR 367; USEPA, 2007a), with monitoring conducted primarily during 2008–2010. UCMR 3 was published on May 2, 2012 (77 FR 26071; USEPA, 2012a), with monitoring conducted primarily during 2013–2015. (The complete analytical monitoring lists are available at: *http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/*.) UCMR 4 was published on December 20, 2016 (81 FR 92666), with monitoring conducted between 2018 and 2020 (final UCMR 4 data is not complete in time for this RD 4 preliminary determination).

The UCMR program is designed as a three-tiered approach for monitoring contaminants related to the availability and complexity of analytical methods, laboratory capacity, sampling frequency, relevant universe of PWSs, and other considerations (*e.g.,* cost/burden). Assessment Monitoring (AM) includes the largest number of PWSs and is generally used when there is sufficient laboratory capacity. The Screening Survey (SS) includes a smaller number of PWSs to conduct monitoring and may be used, for example, when there are possible laboratory capacity issues for the analytical methods required. Pre-Screen Testing (PST) is generally used to collect monitoring information for contaminants with analytical methods that are in an early stage of development, and/or very limited laboratory availability.

The EPA designed the AM sampling frame to ensure that sample results would support a high level of confidence and a low margin of error (see USEPA, 1999 and 2001a, for UCMR design details). AM is required for all large and very large PWSs, those serving between 10,001 and 100,000 people and serving more than 100,000 people, respectively (*i.e.,* a census of all large and very large systems) and a national statistically representative sample of 800 small PWSs, those serving 10,000 or fewer people.[19] PWSs that purchase 100% of their water were not required to participate in UCMR 1 and UCMR 2. However, those systems were not excluded under UCMR 3. All systems that purchase 100% of their water and serve more than 10,000 people were subject to UCMR 3. Systems that purchase 100% of their water and serve a retail population of 10,000 or fewer customers were only required to monitor if they were selected as part of the UCMR 3 nationally representative sample of small systems.

Each system conducts UCMR assessment monitoring for 12-consecutive months (during the three-year monitoring period). The rules typically require quarterly monitoring for surface water systems and twice-a-year, six-month interval monitoring for groundwater systems. At least one sampling event must occur during a specified vulnerable period. Differing sampling points within the PWS may be specified for each contaminant related to the contaminants source(s).

The objective of the UCMR sampling approach for small systems was to collect contaminant occurrence data from a statistically-selected, nationally representative sample of small systems. The small system sample was stratified and population-weighted, and included some other sampling adjustments such as allocating a selection of at least two systems from each state for spatial coverage (the design meets the data quality objective for overall exposure estimates (99% confidence level with ±1% error tolerance, at 1% exposure), while providing more precise occurrence estimates for categories of small systems). The UCMR AM program includes systems from all 50 states, the District of Columbia, all five U.S. territories, and tribal lands across all of the EPA regions. With contaminant monitoring data from all large PWSs—a census of large systems—and a statistical, nationally representative sample of small PWSs, the UCMR AM program provides a robust dataset for evaluating national drinking water contaminant occurrence.

UCMR 1 AM was conducted by approximately 3,090 large systems and 797 small systems. Approximately 33,800 samples were collected for each contaminant. In UCMR 2, sampling was conducted by over 3,300 large systems and 800 small systems and resulted in over 32,000 sample results for each contaminant.

As noted, in addition to AM, SS monitoring was required for contaminants. For UCMR 1, the SS was conducted at 300 PWSs (120 large and 180 small systems) selected at random from the pool of systems required to conduct AM. Samples from the 300 PWSs from throughout the nation provided approximately 2,300 analyses for each contaminant. While the statistical design of the SS is national in scope, the uncertainty in the results for contaminants that have low occurrence is relatively high. Therefore, the EPA looked for additional data to supplement the SS data for regulatory determinations.

For the UCMR 2 SS, the EPA improved the design to include a census of all systems serving more than 100,000 people (approximately 400 PWSs—but the largest portion of the national population served by PWSs) and a nationally representative, statistically selected sample of 320 PWSs serving between 10,001 and 100,000 people, and 480 small PWSs serving 10,000 or fewer people (72 FR 367, January 4, 2007, USEPA, 2007a). With approximately 1,200 systems participating in the SS, sufficient data were generated to provide a confident national estimate of contaminant occurrence and population exposure. In UCMR 2, the 1,200 PWSs provided more than 11,000 to 18,000 analyses (depending on the sampling design for the different contaminants).

For UCMR 3, all large and very large PWSs (serving between 10,001 and 100,000 people and serving more than 100,000 people, respectively), plus a statistically representative national sample of 800 small PWSs (serving

[19] Section 1445 of the Safe Drinking Water Act was recently amended by Public Law 115–270, America's Water Infrastructure Act of 2018 (AWIA), and now specifies that, effective October 23, 2021, subject to the availability of appropriations for such purpose and appropriate laboratory capacity, the EPA must require all systems serving between 3,300 and 10,000 persons to monitor and ensure that only a representative sample of systems serving fewer than 3,300 persons are required to monitor.

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10,000 people or fewer), conducted AM. UCMR 3 SS monitoring was conducted by all large systems serving more than 100,000 people, a nationally representative sample of 320 large systems serving 10,001 to 100,000 people, and a nationally representative sample of 480 small water systems serving 10,000 or fewer people. In contrast to implementation of UCMR 1 and 2 monitoring, transient noncommunity water systems that purchase all their finished water from another system were not excluded from the requirements of UCMR 3 (this was applicable only to PST). See USEPA (2012a) and USEPA (2019b) for more information on the UCMR 3 study design and data analysis.

As previously noted, the details of the occurrence data and the results or findings for each of the contaminants considered for regulatory determination are presented in Section IV.B, the contaminant profiles section, and are described in further detail in the *Regulatory Determination 4 Support Document* (USEPA, 2019a). The national design, statistical sampling frame, any new analytical methods, and the data analysis approach for the UCMR program has been peer-reviewed at different stages of development (see USEPA, 2001b, 2008b, 2015a, 2019b).

(2) National Inorganics and Radionuclides Survey (NIRS)

The EPA conducted the NIRS to provide a statistically representative sample of the national occurrence of 36 selected inorganic compounds (IOCs) and 6 radionuclides in CWSs served by groundwater. The sample was stratified by system size and 989 groundwater CWSs were selected at random representing 49 states (all except Hawaii) as well as Puerto Rico. The survey focused on groundwater systems, in part because IOCs tend to occur more frequently and at higher concentrations in groundwater than in surface water. Each of the selected CWSs was sampled at a single time between 1984 and 1986.

One limitation of the NIRS is a lack of occurrence data for surface water systems. Information about NIRS monitoring and data analysis is available in *The Analysis of Occurrence Data from the Unregulated Contaminant Monitoring (UCM) Program and National Inorganics and Radionuclides Survey (NIRS) in Support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List* (USEPA, 2008c). Another potential limitation of the NIRS is the age of the data. Although the NIRS monitoring occurred nearly 35 years ago, results may still provide insight into current conditions, as the presence of IOCs in aquifers depends in large part on equilibrium with stable natural sources in contiguous rock formations.

(3) Unregulated Contaminant Monitoring (UCM) Program Rounds 1 and 2

In 1987, the EPA initiated the UCM program to fulfill a 1986 SDWA Amendment requirement to monitor for specified unregulated contaminants. The UCM required PWSs serving more than 500 people to conduct monitoring. The EPA implemented the UCM program in two phases or rounds. The first round of UCM monitoring generally extended from 1988 to 1992 and is referred to as UCM Round 1 monitoring. The second round of UCM monitoring generally extended from 1993 to 1997 and is referred to as UCM Round 2 monitoring. Information about UCM monitoring and data analysis is available in *The Analysis of Occurrence Data from the Unregulated Contaminant Monitoring (UCM) Program and National Inorganics and Radionuclides Survey (NIRS) in Support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List* (USEPA, 2008c).

The UCM-State Round 1 dataset contains PWS monitoring results for 62 then-unregulated contaminants (some have since been regulated). These data were collected by 40 states and primacy entities between 1988 and 1992. The Round 2 dataset contains PWS monitoring results for 48 then-unregulated contaminants. These data were collected by 35 states and primacy entities between 1993 and 1997. Since UCM Round 1 and Round 2 data represent different time periods and include occurrence data from different states, the EPA developed separate national cross-sections for each data set. The UCM Round 1 national cross-section, consisting of data from 24 states, includes approximately 3.3 million records from approximately 22,000 unique PWSs. The UCM Round 2 national cross-section, consisting of data from 20 states, includes approximately 3.7 million records from slightly more than 27,000 unique PWSs.

b. Supplemental Sources of Finished Drinking and Ambient Water Occurrence Data

The Agency evaluates several sources of supplemental information related to contaminant occurrence in finished water and ambient and source waters to augment the primary drinking water occurrence data. Some of these sources were part of other Agency information gathering efforts or submitted to the Agency in public comment or suggested by stakeholders during previous CCL and Regulatory Determination efforts. These supplemental data are useful to evaluate the likelihood of contaminant occurrence in drinking water and/or to more fully characterize a contaminant's presence in the environment and potentially in source water, and to evaluate any possible trends or spatial patterns that may need further review. The descriptions that follow do not cover all the sources that the EPA used. For individual contaminants, the EPA reviewed additional published reports and peer-reviewed studies that may have provided the results of monitoring efforts in limited geographic areas. A more detailed discussion of the supplemental sources of information/data that the EPA evaluated and the occurrence data for each contaminant can be found in the *Regulatory Determination 4 Support Document* (USEPA, 2019a).

(1) Individual States' Data

For RD 4, the Agency evaluated data for unregulated contaminants from the second Six-Year Review of regulated contaminants (USEPA, 2009b), the third Six-Year Review of regulated contaminants (USEPA, 2016c), and individual state websites.

To support the second Six-Year Review of regulated contaminants (USEPA, 2009b), the EPA issued an Information Collection Rule (ICR) to collect compliance monitoring data from PWSs for the time period covering 1998–2005. After issuing the ICR, the EPA received monitoring data from 45 states plus Region 8 and Region 9 Tribes. Six states and Region 9 tribes also provided monitoring data for unregulated contaminants along with their compliance monitoring data. The EPA further collected additional unregulated contaminant data from two additional States that provide monitoring data through their websites.

To support the third Six-Year Review of regulated contaminants (USEPA, 2016c), the EPA issued an ICR to collect compliance monitoring data from PWSs for 2006–2011. After issuing the ICR, 46 states and 8 other primacy agencies provided compliance monitoring data. Nine states, three tribes, Washington, DC, and American Samoa also provided monitoring data for unregulated contaminants along with their compliance monitoring data.

The EPA supplemented these occurrence data for unregulated contaminants by downloading additional and more recent publicly available monitoring data from state websites. Drinking water monitoring

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data for select contaminants were available online from several states, including California, Colorado, Michigan, New Hampshire, New Jersey, and North Carolina. Very limited data were also available from Pennsylvania and Washington. The available state data are varied in terms of quantity and coverage. In many cases they represent targeted monitoring.

These datasets vary from state to state in the contaminants included, the number of samples, and the completeness of monitoring. They were reviewed and used to augment the national data and assessed if they provide supportive observations or any unique occurrence results that might warrant further review.

(2) Community Water System Survey (CWSS)

The EPA periodically conducts the CWSS to collect data on the financial and operating characteristics from a nationally representative sample of CWSs. As part of the CWSS, all systems serving more than 500,000 people receive the survey. In the 2000 and 2006 CWSS, these very large systems were asked questions about the occurrence and concentrations of unregulated contaminants in their raw and finished water. The 2000 CWSS (USEPA, 2002a, 2002b) requested data from 83 very large CWSs and the 2006 CWSS (USEPA, 2009c, 2009d) requested data from 94 very large CWSs. Not all systems answered every question or provided complete information on the unregulated contaminants. Because reported results are incomplete, they are illustrative, not representative, and are only used as supplemental information.

(3) United States Department of Agriculture (USDA) Pesticide Data Program (PDP)

Since 1991, the USDA PDP has gathered data on pesticide residues in food. In 2001 the program expanded to include sampling of pesticide residues in treated drinking water, and in 2004 some sampling of raw water was incorporated as well. The PDP drinking water project continued until 2013 (USDA, 2018). The CWSs selected for sampling tended to be small and medium-sized surface water systems (serving under 50,000 people) located in regions of heavy agriculture. The sampling frame was designed to monitor in regions of interest for at least two years to reflect the seasonal and climatic variability during growing seasons. PDP worked with the EPA to identify specific water treatment facilities where monitoring data were collected. The number of sites and samples varied among different sampling periods. The EPA reviewed the PDP data on the occurrence of select contaminants in untreated and treated water (USDA, 2018).

(4) USGS Pilot Monitoring Program (PMP)

In 1999, USGS and the EPA conducted the PMP to provide information on pesticide concentrations in small drinking water supply reservoirs in areas with high pesticide use (Blomquist et al., 2001). The study was undertaken, in part, to test and refine the sampling approach for pesticides in such reservoirs and related drinking water sources. Sampling sites represent a variety of geographic regions, as well as different cropping patterns. Twelve water supply reservoirs considered vulnerable to pesticide contamination were included in the study. Samples were collected quarterly throughout the year and at weekly or biweekly intervals following the primary pesticide-application periods. Water samples were collected from the raw water intake and from finished drinking water taps prior to entering the distribution system. At some sites, samples were also collected at the reservoir outflow.

(5) USGS National Water Quality Assessment (NAWQA)

The USGS instituted the National Water Quality Assessment (NAWQA) program in 1991 to examine ambient water quality status and trends in the United States. The NAWQA program is designed to apply nationally consistent methods to provide a consistent basis for comparisons over time and among significant watersheds and aquifers across the country. These occurrence assessments serve to facilitate interpretation of natural and anthropogenic factors affecting national water quality. The NAWQA program monitors the occurrence of chemicals such as pesticides, nutrients, volatile organic compounds (VOCs), trace elements, radionuclides, hormones and pharmaceuticals, and the condition of aquatic habitats and fish, insects, and algal communities. For more detailed information on the NAWQA program design and implementation, please refer to Leahy and Thompson (1994), Hamilton et al. (2004), and NRC (2012).

The NAWQA program has been designed in ten-year cycles to enable national coverage that can be used for trends and causal assessments. In the Cycle 1 monitoring period, which was conducted from 1991 through 2001, NAWQA collected data from over 6,400 surface water and 6,300 groundwater sampling points. Cycle 2 monitoring covers the period from 2002 through 2012, with various design changes from Cycle 1 (see Hamilton et al., 2004). Sampling for Cycle 3 is currently underway (2013–2023). Surface water monitoring will be conducted at 313 sites while groundwater assessments will be designed to evaluate status and trends at the principal aquifer and national scales. Refer to Rowe et al. (2010; 2013) for more details.

The EPA performed a summary analysis of the Cycle 1, Cycle 2, and available Cycle 3 water monitoring data for the Regulatory Determination process. The surface water data consisted of river and stream samples; for groundwater, all well data were used.

For RD 4, the EPA used and evaluated many USGS NAWQA reports to review causal or spatial factors that USGS may have presented in their interpretations. In particular, the EPA evaluated many reports from the Pesticide National Synthesis Programs (*e.g.,* Gilliom et al., 2007) and the VOC National Synthesis (*e.g.,* Delzer and Ivahnenko, 2003). While there is overlap in the data used in the USGS reports and the EPA analysis, the USGS reports can provide unique observations related to their synthesis of additional data.

For RD 4, the EPA also supplemented these data with information from recent special USGS reports that also used additional data from other programs, particularly reports that focused on contaminant occurrence in source waters for PWSs, such as: Organic compounds in source water of selected CWSs (Hopple et al., 2009 and Kingsbury et al., 2008); water quality in public-supply wells (Toccalino et al., 2010); water quality in domestic wells and principal aquifers (DeSimone, 2009 and DeSimone et al., 2014); nationwide reconnaissance of contaminants of emerging concern (Glassmeyer et al., 2017); water quality in select CWSs (Grady and Casey, 2001); water quality in carbonate aquifers (Lindsey et al., 2008); VOCs in domestic wells (Moran et al., 2002 and Rowe et al., 2007); and VOCs in the nation's groundwater (Zogorski et al., 2006).

(6) National Water Information System (NWIS)

For RD 4, the EPA evaluated contaminant monitoring results from the non-NAWQA data in the National Water Information System (NWIS) (USGS, 2016). NWIS houses the NAWQA data (described above) and includes other USGS data from unspecified projects. The non-NAWQA NWIS data were analyzed separately from NAWQA data.

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Although NWIS is comprised of primarily ambient water data, some finished drinking water data are included as well. The non-NAWQA data housed in NWIS generally involve fewer constituents per sample than the NAWQA data. Unlike the NAQWA data, the non-NAWQA data are a miscellaneous collection, so they are not as well-suited for making temporal and geographic comparisons. Most NWIS data are available via the Water Quality Portal (see below).

(7) Water Quality Exchange (WQX)/ Water Quality Portal Data System (Formerly STORET)

The EPA's Water Quality Exchange (WQX) is the data format and mechanism for publishing monitoring data available through the Water Quality Portal. WQX replaces the Storage and Retrieval Data System (STORET) as the mechanism for data partners to submit water monitoring data to the EPA. The Water Quality Portal is the mechanism for anyone, including the public, to retrieve water monitoring data from the EPA WQX/STORET, USDA STEWARDS, and USGS NWIS/ BIODATA. The WQX database contains raw biological, chemical, and physical data from surface and groundwater sampling conducted by federal, state and local agencies, Native American Tribes, volunteer groups, academics, and others. WQX includes data from monitoring locations in all 50 states as well as multiple territories and jurisdictions of the United States. Most data are from ambient waters, but in some cases finished drinking water data are included as well. Data owners are responsible for providing data of documented quality, so that data users can choose to access only those data collected and analyzed with data quality objectives that meet their study needs. For more general WQX data information, please refer to: *https://www.epa.gov/waterdata/water-quality-data-wqx.* To retrieve the data, please refer to: *https://www.waterqualitydata.us/portal/.*

c. Supplemental Production, Use, and Release Data

The Agency reviews various sources of information to assess if there are changes or trends in a contaminant's production, use, and release that may affect its presence in the environment and potential occurrence in drinking water. The cancellation of a pesticide or a clear increase in production and use of a contaminant are trends that can inform the regulatory determination process. Several sources are described below. A more detailed discussion of the supplemental sources of information/data that the EPA evaluated and the occurrence data for each contaminant can be found in the *Regulatory Determination 4 Support Document* (USEPA, 2019a).

(1) Inventory Update Reporting (IUR) and Chemical Data Reporting (CDR) Program

The IUR regulation required manufacturers and importers of certain chemical substances, included on the Toxic Substances Control Act (TSCA) Chemical Substance Inventory, to report site and manufacturing information and the amount of chemicals produced or imported in amounts of 25,000 pounds or more at a single site. Additional information on domestic processing and use was required to be reported for chemicals produced or imported in amounts of 300,000 pounds or more at a single site. Prior to the 2003 TSCA Amendments (*i.e.,* reporting from 2002 or earlier), information was collected for only organic chemicals that were produced or imported in amounts of 10,000 pounds or more, and was limited to more basic manufacturing information such as production volume. In 2011 the Agency issued the CDR Rule, which replaced the IUR Rule and established a somewhat modified program, including annual data gathering and periodic reporting. CDR makes use of a two-tiered system of reporting thresholds, with 25,000 pounds the threshold for some contaminants and 2,500 pounds the threshold for others. Contaminants may have reports for some years but not others (USEPA, 2008d; USEPA, 2016d).

(2) Toxics Release Inventory (TRI)

The EPA established the Toxics Release Inventory (TRI) in 1987 in response to Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA). EPCRA Section 313 requires facilities to report annual information on toxic chemical releases from facilities that meet reporting criteria to both the EPA and the states. The TRI database details not only the types and quantities of toxic chemicals released to the air, water, and land by facilities, but also provides information on the quantities of chemicals sent to other facilities for further management (USEPA, 2003b; USEPA, 2019c). Currently, for most chemicals, reporting of releases is required if 25,000 pounds or more of the chemical are manufactured or processed at a facility, or if 10,000 pounds or more are used at the facility. For certain chemicals the reporting threshold is as low as 0.1 grams, 10 pounds, or 100 pounds (40 CFR 372.28). Both the number and type of facilities required to report has increased over time. Information from the TRI was downloaded in 2017 (USEPA, 2017a).

Although TRI can provide a general idea of release trends, these trends should be interpreted with caution since the list of chemicals with reporting requirements has generally increased over time. In addition, only those facilities that meet specific criteria are required to report to the TRI program. Finally, data on releases cannot be used as a direct measure of public exposure to a chemical in drinking water (USEPA, 2019a).

(3) Pesticide Usage Estimates

For the regulatory determinations process, the Agency reviews various sources of information about pesticide usage. Pesticide use and manufacturing information is considered confidential business information (CBI) and therefore, accurate measures of production and use are not publicly available. As a result, the Agency reviews various estimates of use as supplemental information in the deliberative process.

For some pesticides, the EPA presents estimations of annual U.S. usage of individual pesticides in its pesticide reregistration documents (*e.g.,* REDs, IREDs, TREDs). The EPA also periodically issues Pesticides Industry Sales and Usage reports. The reports provide contemporary and historical information on U.S. pesticide production, imports, exports, usage, and sales, particularly with respect to dollar values and quantities of active ingredient (USEPA, 2004a; USEPA, 2011c; USEPA, 2017b).

The National Center for Food and Agricultural Policy (NCFAP), a private non-profit institution, has also produced national pesticide use estimates based on USDA state-level statistics and surveys for commercial agriculture usage patterns and state-level crop acreage. The database contains estimates of pounds applied and acres treated in each State for 220 active (pesticide) ingredients and 87 crops. The majority of the chemicals monitored are herbicides, but the database also follows significant numbers of fungicides and insecticides (NCFAP, 2000).

The USGS produced usage estimates and maps for over 200 pesticides used in United States crop production, providing spatial insight to the regional use of many pesticides (USGS, 2018). These pesticide use estimates were generated by the USGS using data from proprietary surveys of farm operations, USDA Census of Agriculture, and other

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sources. USGS used two methods to estimate pesticide usage, since pesticide usage information was not available in some districts. ''EPest-High'' estimates were generated by projecting usage estimates for such districts based on usage in neighboring districts. ''EPest-Low'' estimates were generated by assuming no usage in such districts.

IV. Contaminant-Specific Discussions for the RD 4 Preliminary Determination

A. Summary of the Preliminary Regulatory Determination

Based on the EPA's evaluation of the three SDWA criteria (discussed in section II.B.1), the Agency is making preliminary determinations to regulate two contaminants and to not regulate six contaminants. For each of the eight contaminants discussed in this section of this document, Table 7 summarizes information about the health assessment, principle study, critical effects, and associated reference dose and/or cancer slope factor used to derive an HRL. Following Table 7, Table 8 summarizes the primary occurrence information used to make these preliminary regulatory determinations. Section IV.B of this document provides a more detailed summary of the information and the rationale used by the Agency to reach its preliminary decisions for these eight contaminants. For more information about the two Phase 3 contaminants that are not receiving a preliminary regulatory determination, see section V.

TABLE 7—HEALTH EFFECTS INFORMATION FOR CONTAMINANTS DISCUSSED IN SECTION IV OF THIS DOCUMENT

RD 4 contaminant	Health assessment	Principle study	Critical effect	RfD for noncancer effects, in mg/kg/day	Cancer slope factor, in $(mg/kg/day)^{-1}$	HRL, in µg/L
PFOS	EPA OW HESD, 2016.	Luebker et al. 2005a and 2005b.	decreased neonatal rat body weight	0.00002	n/a	0.07.
PFOA	EPA OW HESD, 2016.	Lau et al., 2006	reduced ossification in proximal phalanges and accelerated puberty in male pups, in mice.	0.00002	[20] 0.07	0.07.
1,1-Dichloroethane	EPA ORD PPRTV, 2006.	Muralidhara et al., 2001.	increased urinary enzyme markers for renal damage and central nervous system (CNS) depression in rats.	0.2	n/a	1,000.
Acetochlor	EPA OPP HHRA, 2018.	ICI, Inc. 1988	increased salivation, increased alanine aminotransferase (ALT), ornithine carbamyl transferase and triglyceride levels; decreased blood glucose; and histopathological changes in the kidneys, liver and testes of males, in beagle dogs.	0.02	n/a	100.
Methyl Bromide (Bromomethane).	EPA OPP HHRA, 2006.	Mertens, 1997	decreased body weight, decreased rate of body weight gain, and decreased food consumption in rats.	0.022	n/a	100.
Metolachlor	EPA OPP HHRA, 2018.	Page, 1981	decreased pup body weight in rats	0.26	n/a	300.
Nitrobenzene	EPA IRIS, 2009	NTP, 1983	changes in absolute and relative organ weights, splenic congestion, and increases in reticulocyte count and metHb concentration in rats.	0.002	n/a	10.
RDX	EPA IRIS, 2018	Crouse et al., 2006 (noncancer); Lish et al. 1984 (cancer).	convulsions in rats (noncancer); lung and liver tumors in mice (cancer).	0.004	0.08	30 (noncancer); 0.4 (cancer).

TABLE 8—OCCURRENCE FINDINGS FROM PRIMARY DATA SOURCES

RD 4 contaminant	HRL, µg/L	Primary database	PWSs with at least 1 detection > ½ HRL	Population served by PWSs with at least 1 detection > ½ HRL	PWSs with at least 1 detection > HRL	Population served by PWSs with at least 1 detection > HRL
PFOS	0.07	UCMR 3 AM	95/4,920 (1.93%)	10,427,193/241 M (4.32%)	46/4,920 (0.93%)	3,789,831/241 M (1.57%).
PFOA	0.07	UCMR 3 AM	53/4,920 (1.07%)	3,652,995/241 M (1.51%)	13/4,920 (0.26%)	490,480/241 M (0.20%).
1,1-Dichloroethane.	1,000	UCMR 3 AM	0/4,916 (0.00%)	0/241 M (0.00%)	0/4,916 (0.00%)	0/241 M (0.00%).
Acetochlor	100	UCMR 1 AM	0/3,869 (0.00%)—UCMR 1	0/226 M (0.00%)—UCMR 1.	0/3,869 (0.00%)—UCMR 1	0/226 M (0.00%)—UCMR 1.
		UCMR 2 SS	0/1,198 (0.00%)—UCMR 2	0/157 M (0.00%)—UCMR 2.	0/1,198 (0.00%)—UCMR 2	0/157 M (0.00%)—UCMR 2.
Methyl Bromide (Bromomethane).	100	UCMR 3 AM	0/4,916 (0.00%)	0/241 M (0.00%)	0/4,916 (0.00%)	0/241 M (0.00%).
Metolachlor	300	UCMR 2 SS	0/1,198 (0.00%)	0/157 M (0.00%)	0/1,198 (0.00%)	0/157 M (0.00%).
Nitrobenzene	10	UCMR 1 AM	2/3,861 (0.05%)	255,358/226 M (0.11%)	2/3,861 (0.05%)	255,358/226 M (0.11%).
RDX	30, 0.4	UCMR 2 AM	0/4,139 (0.00%) > 15 µg/L	0/229 M (0.00%) > 15 µg/L.	0/4,139 (0.00%) > 30 µg/L	0/229 M (0.00%) > 30 µg/L.

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TABLE 8—OCCURRENCE FINDINGS FROM PRIMARY DATA SOURCES—Continued

RD 4 contaminant	HRL, µg/L	Primary database	PWSs with at least 1 detection > ½ HRL	Population served by PWSs with at least 1 detection > ½ HRL	PWSs with at least 1 detection > HRL	Population served by PWSs with at least 1 detection > HRL
			3/4,139 (0.07%) > 0.2 µg/L.	96,033/229 M (0.04%) > 0.2 µg/L.	3/4,139 (0.07%) > 0.4 µg/L.	96,033/229 M (0.04%) > 0.4 µg/L.

B.Contaminant Profiles

1. Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA)

a. Background

PFAS are a group of synthetic chemicals that have been in use since the 1940s. PFAS are found in a wide array of consumer and industrial products. PFAS manufacturing and processing facilities, facilities using PFAS in production of other products, airports, and military installations have been associated with PFAS releases into the air, soil, and water (USEPA, 2016e; USEPA, 2016f).

PFOS and PFOA—two of the most widely-studied and longest-used PFAS—are part of a subset of PFAS known as perfluorinated alkyl acids (PFAA). These two compounds have been detected in up to 98% of serum samples taken in biomonitoring studies that are representative of the U.S. general population; however, since PFOA and PFOS have been voluntarily phased out in the U.S., serum concentrations have been declining (CDC, 2019). The National Health and Nutrition Examination Survey (NHANES) data shows that 95th-percentile serum PFOS concentrations have decreased from 75.7 µg/L in the 1999–2000 cycle to 18.3 µg/L in the 2015–2016 cycle (CDC, 2019; Jain, 2018; Calafat et al., 2007; Calafat et al., 2019), a decrease of over 75 percent. In early 2000, the EPA worked with the 3M Company, which was the only major manufacturer of PFOS in the United States at that time, to support the company's voluntary phase-out and elimination of PFOS production and use. Under the EPA's 2010/2015 PFOA Stewardship Program, eight major chemical manufacturers and processors agreed to phase out the use of PFOA and PFOA-related chemicals in their products and emissions from their facilities. All companies met the PFOA Stewardship Program goals by 2015. While companies participating in the PFOA Stewardship program report that they no longer produce or use PFOA domestically, PFOA may still be produced domestically or imported or used by companies not participating in the PFOA Stewardship Program. In addition, PFOA and PFOS can also be present in imported articles (USEPA, 2017c). Due to the widespread use and persistence of PFAS in the environment, most people have been exposed to PFAS, including PFOA and PFOS (USEPA, 2016e; USEPA, 2016f).

Production of PFOA and PFOS is subject to CDR reporting. Production volumes of PFOA and PFOS were claimed by reporting companies as confidential for the most recent reporting cycles. The last time production (including import) of PFOA exceeded the CDR reporting threshold was during the 2016 reporting cycles (which includes production information from 2012–2015) and it was phased out by companies participating in the 2010/2015 PFOA Stewardship Program in 2013. Similarly, PFOS was phased out by 3M in 2002 and the most recently reported data for PFOS are from the 2002 reporting cycle (which includes production information from 2001 only) (USEPA, 2019a). Absence of recent reporting may indicate that production (including import) of PFOA and PFOS has halted or has been below the CDR reporting thresholds. Although PFOA and PFOS are not produced domestically or imported by the companies participating in the 2010/2015 PFOA Stewardship Program, PFOA and PFOS may still be produced domestically or imported below the CDR reporting thresholds (*i.e.,* 2,500 pounds) by companies not participating in the PFOA Stewardship Program.

b. Statutory Criterion #1 (Adverse Health Effects)

The EPA is preliminarily determining that PFOA and PFOS meet the SDWA statutory criterion #1 for regulatory determinations: They may have adverse effects on the health of persons. In 2016, the EPA published health assessments (health effects support documents or HESDs) for PFOA and PFOS based on the Agency's evaluation of the peer reviewed science available at that time. This section presents a summary of the adverse health effects discussed in the HESDs. For specific details on the potential for adverse health effects and approaches used to identify and evaluate information on hazard and dose-response, please see USEPA (2016d), USEPA (2016e), USEPA (2016f), and USEPA (2016g). The lifetime HA of 0.07 µg/L is used as the HRL for Regulatory Determination 4.

Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney). The associations for most epidemiology endpoints are mixed. Although mean serum values are presented in the human studies, actual estimates of PFOA exposure (*i.e.,* doses/duration) are not currently available. Thus, the serum level at which the effects were first manifest and whether the serum had achieved steady state at the point the effect occurred cannot be determined. It is likely that some of the human exposures that contribute to serum PFOA values come from PFOA derivatives or precursors that break down metabolically to PFOA. These compounds could originate from PFOA in diet and materials used in the home, which creates potential for confounding. In addition, most of the subjects of the epidemiology studies have many PFASs and/or other contaminants in their blood. Although the study designs adjust for other potential toxicants as confounding factors, their presence constitutes a level of uncertainty that is usually absent in the animal studies. Taken together, the weight of evidence for human studies supports the conclusion that PFOA exposure is a human health hazard. At this time, EPA concludes that the human studies are adequate for use qualitatively in the identification hazard and are supportive of the findings in laboratory animals.

[20] Using the CSF, the calculated concentration in drinking water with one-in-a-million risk for an increase in testicular tumors at levels greater than background is 0.0005 mg/L.

The equivalent concentration derived from the RfD is lower than the concentration of 0.0005 mg/L associated with a one-in-a-million risk for testicular cancer indicating that a guideline derived from the developmental endpoint will be protective for the cancer endpoint. (USEPA, 2016g).

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For PFOA, oral animal studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats and mice. These animal studies report developmental effects (survival, body weight changes, reduced ossification, delays in eye opening, altered puberty, and retarded mammary gland development), liver toxicity (hypertrophy, necrosis, and effects on the metabolism and deposition of dietary lipids), kidney toxicity (weight), immune effects, and cancer (liver, testicular, and pancreatic) (USEPA, 2016e). Overall, the animal toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity. Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney). Overall, the developmental toxicity studies in animals available for PFOA demonstrate that the developing rodent fetus and newborn rodent are sensitive to PFOA-induced toxicity.

PFOA is known to be transmitted to the fetus via cord blood and to the newborn, infant, and child via breast milk (USEPA, 2016f). Under the EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005b), there is ''suggestive evidence of carcinogenic potential'' for PFOA. Similarly, the International Agency for Research on Cancer (IARC) classifies PFOA as ''possibly carcinogenic to humans'' (IARC, 2019a; IARC, 2019b).

The EPA calculated several candidate RfDs for PFOA in the 2016 HESD and selected the RfD of 0.00002 mg/kg/day based on reduced ossification in proximal phalanges and accelerated puberty in male pups following exposure during gestation and lactation in a developmental toxicity study in mice (Lau et al., 2006) for the derivation of a lifetime HA. The RfD for PFOA was calculated by applying uncertainty factors to account for interspecies variability (3), intraspecies differences (10), and use of a LOAEL (3). The Health Effects Support Document (USEPA, 2016h) describes these uncertainties in Section 4. Additionally, uncertainties and limitations (*i.e.,* human epidemiological data, immunological and mammary gland endpoints, and exposure) are discussed in detail in Section 8 of the Health Advisory (USEPA, 2016f) document. The lifetime HA of 0.07 µg/L was calculated using the 0.00002 mg/kg/day RfD for developmental effects, a DWI to BW ratio for the 90th percentile [21] for lactating women (0.054 L/kg/day) and a calculated 20% RSC (USEPA, 2016f). This RfD is protective of effects other than those occurring during development such as kidney and immune effects. Because of the potential for increased susceptibility during the time period of pregnancy and lactation observed in this study, the EPA used DWI and BW parameters for lactating women in the calculation of a lifetime HA for this target population during this potential critical time period. The EPA also calculated a CSF of 0.07 $(mg/kg/day)^{-1}$ based on testicular tumors in rats. The resultant HA using this CSF is greater than the lifetime HA based on noncancer effects, indicating that the HA derived based on the developmental endpoint is protective for the cancer endpoint (USEPA, 2016h).

For PFOS, epidemiological studies have reported associations between PFOS exposure and high serum cholesterol and reproductive and developmental parameters. The strongest associations are related to serum lipids with increased total serum cholesterol and high-density lipoproteins (HDLs). As with PFOA, the associations for most epidemiology endpoints are inconsistent. Although mean serum values are presented in the human studies, actual estimates of PFOS exposure (*i.e.,* doses/duration) are not currently available. Thus, the serum level at which the effects were first manifest and whether the serum had achieved steady state at the point the effect occurred cannot be determined (USEPA, 2016e) Human epidemiological studies suggest an association between higher PFOS levels and decreases in female fecundity and fertility, decreased birth weights in offspring and other measures of postnatal growth (*e.g.,* small for gestational age).

Short-term and chronic exposure studies in animals demonstrate increases in liver weight consistently. Co-occurring effects in these studies include decreased cholesterol, hepatic steatosis, lower body weight, and liver histopathology. One and two generation toxicity studies also show decreased pup survival and body weights. Additionally, developmental neurotoxicity studies show increased motor activity and decreased habituation and increased escape latency in the water maze test following in utero and lactational exposure to PFOS. Gestational and lactational exposures were also associated with higher serum glucose levels and evidence of insulin resistance in adult offspring. Limited evidence suggests immunological effects in mice. Short-term and subchronic duration studies are available in multiple animal species including monkeys, rats and mice. These studies also found increased serum glucose levels and insulin resistance in adult animals exposed during development, developmental effects (decreased body weight and survival), reproductive effects (impacts on mating behavior), liver toxicity (increased liver weight co-occurring with decreased serum cholesterol, hepatic steatosis), developmental neurotoxicity (impaired spatial learning and memory), suppressed immunological responses, and cancer (thyroid and liver). Increased incidence of hepatocellular adenomas in the male (12% at the high dose) and female rats (8% at the high dose) and combined adenomas/carcinomas in the females (10% at the high dose) were observed, but they did not display a clear dose-related response; Thyroid tumors (adenomas and carcinomas) were seen in males receiving 0, 0.5, 2, 5, or 20 ppm and in females receiving 5 or 20 ppm in their diet. The tumor (adenomas + carcinomas) prevalence for males was consistent across dose groups. In males the incidence of thyroid tumors was significantly elevated only in the high-dose, recovery group males exposed for 52 weeks (10/39) but not in the animals receiving the same dose at 105 weeks. There were very few follicular cell adenomas/carcinomas in the females (5 total) with no dose-response. The most frequent thyroid tumor type in the females was C-cell adenomas, but the highest incidence was that for the controls and there was a lack of dose response among the exposed groups. C-cell adenomas were not observed in males (Thomford 2002; Butenhoff et al. 2012). Overall, the animal toxicity studies available for PFOS demonstrate that the developing fetus and newborn rodent are sensitive to PFOS induced toxicity. PFOS is known to be transmitted to the fetus via cord blood and to the newborn, infant, and child via breast milk (USEPA, 2016f). Applying the EPA *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005b), there is suggestive evidence of carcinogenic potential for PFOS. However, the weight of evidence for humans is too limited to support a quantitative cancer assessment given that there was no evidence for dose-response from which to derive a slope factor for the tumor types identified in animals.

[21] Consumers only estimate of combined direct and indirect community water ingestion; see Table 3–81 in USEPA, 2011b.

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The EPA calculated multiple candidate RfDs for PFOS in the HESD and selected the RfD of 0.00002 mg/kg/day based on decreased neonatal rat body weight from both the one- and two-generation studies by Luebker et al. (2005a, 2005b) for the derivation of a lifetime HA. The RfD for PFOS was calculated by applying uncertainty factors to account for interspecies variability (3) and intraspecies differences (10). The Health Effects Support Document (USEPA, 2016g) describes these uncertainties in Section 4. Additionally, uncertainties and limitations (*i.e.,* human epidemiologic data, immunological and mammary gland endpoints, and exposure) are discussed in detail in Section 8 of the Health Advisory (USEPA, 2016e) document. The lifetime HA of 0.07 µg/L was calculated using the 0.00002 mg/kg/day RfD for developmental effects, a DWI to BW ratio for the 90th percentile [21] for lactating women (0.054 L/kg/day) and a 20% RSC (USEPA, 2016e). The lifetime HA of 0.07 µg/L is used as the HRL for Regulatory Determination 4.

The RfDs for both PFOA and PFOS are both based on developmental effects and are numerically identical. Thus, when both chemicals co-occur at the same time and location, the EPA recommended a conservative and health-protective approach of 0.07 µg/L for the PFOA/PFOS total combined concentration (USEPA, 2016e).

The EPA has initiated a systematic literature review of peer-reviewed scientific literature for PFOA and PFOS published since 2013 with the goal of identifying any new studies that may be relevant to human health assessment. An annotated bibliography of identified studies as well as the protocol used to identify the relevant publications can be found in Appendix D of the *Regulatory Determination 4 Support Document* (USEPA, 2019a), available in the docket for this document. Additional analyses of these new studies is needed to confirm relevance, extract the data to assess the weight of evidence, and identify critical studies in order to inform future decision making. The EPA is seeking comment on any additional studies and information that it should consider. Should the EPA make a final positive regulatory determination for PFOA and PFOS, the Agency will undertake the SDWA rulemaking process to establish a National Primary Drinking Water Regulation for those contaminants. For that rulemaking effort, in addition to using the best available science, the SDWA requires that the Agency seek recommendations from the EPA Science Advisory Board, and consider public comment on any proposed rule. Therefore, EPA anticipates further scientific review of new science prior to promulgation of any regulatory standard.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA is preliminarily determining that PFOA and PFOS meet the SDWA statutory criterion #2 for regulatory determinations: they occur with a frequency and at levels of public health concern at PWSs based on the EPA's evaluation of the available occurrence information. The EPA is seeking public comment on whether the data described below support such a determination and whether additional data or studies exist which EPA should consider when finalizing a determination.

EPA has made its preliminary determination based, in part, on the UCMR 3 data (USEPA, 2019b). The EPA has determined in accordance with SDWA 1412(b)(1)(B)(ii)(II) that the UCMR 3 data are the best available occurrence information for the PFOA/PFOS regulatory determinations. UCMR 3 monitoring occurred between 2013 and 2015and currently represents the only nationally-representative finished water dataset for PFOA and PFOS. Under UCMR 3, 36,972 samples from 4,920 PWSs were analyzed for PFOA and PFOS. The MRL for PFOA was 0.02 µg/L and the MRL for PFOS was 0.04 µg/L. A total of 1.37% of samples had reported detections (greater than or equal to the MRL) of at least one of the two compounds. To examine the occurrence of PFOS and PFOA in aggregate, the EPA summed the concentrations detected in the same sample to calculate a total PFOS/PFOA concentration.

The EPA notes that when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations (USEPA, 2016g; USEPA, 2016h). The Regulatory Determination 4 Support Document presents a sample-level summary of the results for the individual contaminants (USEPA, 2019a). Concentrations of PFOS or PFOA below their respective MRLs were set equal to 0 µg/L when calculating the total PFOS/PFOA concentration for the sample. The maximum summed concentration of PFOA and PFOS was 7.22 µg/L and the median summed value was 0.05 µg/L. Summed PFOA and PFOS concentrations exceeded the HRL (0.07 µg/L) at a minimum of 1.3% of PWSs (63 PWSs [22]). Since UCMR 3 monitoring occurred, certain sites where elevated levels of PFOA and PFOS were detected may have installed treatment for PFOA and PFOS, may have chosen to blend water from multiple sources, or may have otherwise remediated known sources of contamination. Those 63 PWSs serve a total population of approximately 5.6 million people and are located in 25 states, tribes, or U.S. territories (USEPA, 2019b). The HRLs for PFOA and PFOS are based on the 2016 drinking water Health Advisories and reflect concentrations of PFOA and PFOS in drinking water at which adverse health effects are not anticipated to occur over a lifetime (USEPA, 2016e; USEPA, 2016f).

Consistent with the Agency's commitment in the PFAS Action Plan (USEPA, 2019d) to present information about additional sampling for PFAS in water systems, the EPA has supplemented its UCMR data with data collected by states who have made their data publicly available at this time. In some cases, EPA obtained the data directly from the state's public website while, in others, these data were provided to EPA. Specifically, the EPA evaluated publicly available monitoring data that permitted summed PFOA and PFOS analyses from the state websites of New Hampshire, Colorado, and Michigan. Additional finished drinking water monitoring data was provided to the EPA by the New Jersey Department of Environmental Protection. These data are summarized in Table 9 below. The EPA notes that some of these data are from targeted sampling efforts and thus may not be representative of occurrence in the state. The EPA also notes that states which chose to make their occurrence data publicly available and the state that chose to provide its data to the EPA may not necessarily represent occurrence in other states. The Regulatory Determination 4 Support Document presents a detailed discussion of additional information from states on occurrence of these contaminants in drinking water systems (USEPA, 2019a). The EPA is also aware that some of these states may have updated data available and that additional states have or intend to conduct monitoring of finished drinking water, such as Illinois, Pennsylvania, and Vermont. The EPA will consider any data submitted in response to this proposal to inform future regulatory decision making. The EPA is also aware of additional locations with drinking

[22] Sum of PFOA + PFOS results rounded to 2 decimal places in those cases where a laboratory reported more digits.

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water impacts (including private wells) from contaminated sites. These include sites near production facilities, active and former military bases, and other point sources.[23]

For the following summed PFOA and PFOS analyses, monitoring data sets from public water systems in New Hampshire and New Jersey permitted combined analysis of PFOS and PFOA occurrence (*i.e.,* with paired PFOS and PFOA concentrations reported for each individual water sample). In addition, Colorado and Michigan directly reported monitoring results for combined PFOS and PFOA. All states data sets summarized in Table 9 had at least one instance of summed PFOS and PFOA concentrations greater than the HRL of 0.07 μg/L. Additional details can be found in the *Regulatory Determination 4 Support Document* (USEPA, 2019a).

TABLE 9—COMBINED PFOS AND PFOA OCCURRENCE: SUMMARY OF STATE MONITORING RESULTS[24]

State (reference)	Date range	Type of water tested	Notes on coverage	Summary of results	Survey type
Colorado (CDPHE, 2018)	2013–2017.	Surface Water (Finished Water) and Drinking Water Distribution Samples.	Data available from 28 ''drinking water distribution zones'' (one or more per public water system) in targeted sampling efforts at a known contaminated aquifer region. Data were collected by El Paso County Public Health, local water districts and utilities, and the Colorado Department of Public Health and Environment (CDPHE). Results represent data collected in a targeted region. Detection limits ranged from 0.002 μg/L to 0.040 μg/L.	The maximum summed concentration of PFOA and PFOS was 0.3 μg/L and the median summed value was 0.09 μg/L. Summed PFOA and PFOS concentrations exceeded the EPA HRL (0.07 μg/L) at 25% of distribution zones (7 distribution zones).	Targeted.
Michigan (Michigan EGLE, 2019)	2018–2019.	Groundwater and Surface Water—Raw and Finished Water (Community Water Supplies).	Data available from 1,119 public community water systems, downloaded in October 2019. Results are from the Michigan Department of Environment, Great Lakes and Energy (EGLE) statewide sampling efforts for PFAS of drinking water from community water supplies. Results are presented for the sum of PFOA and PFOS concentrations. Information on detection limits was not available.	The maximum summed concentration of PFOA and PFOS was 1.52 μg/L and the median summed value was 0.004 μg/L. Summed PFOA and PFOS concentrations exceeded the EPA HRL (0.07 μg/L) at 0.09% of PWSs (1 PWS).	Statewide.
New Hampshire (NHDES, 2017)	2013–2017.	Groundwater and Surface Water.	Data available online from 295 PWSs providing results to NH, including PWSs near contaminated sites. Results represent all PFOA and PFOS water quality data reported to New Hampshire Department of Environmental Services (NHDES) through May 3, 2017. There is no discussion of representativeness. Detection limits ranged from 0.0005 μg/L to 0.04 μg/L.	The maximum summed concentration of PFOA and PFOS was 0.242 μg/L and the median summed value was 0.006 μg/L. Summed PFOA and PFOS concentrations exceeded the EPA HRL (0.07 μg/L) at 1.01% of PWSs (3 PWSs).	Targeted.
New Jersey (NJDEP, 2019)	2019 ...	Groundwater and Surface Water—Finished Water.	Statewide sampling of finished drinking water data between January 1, 2019 and June 28, 2019. These represent the first two quarters of statewide efforts to sample of finished drinking water. Under this sampling effort, 2,459 water samples from 1,049 PWS were analyzed for PFOA and PFOS. Detection limits ranged from 0.0016 - 0.0046 (doesn't specify for which PFAS compound).	The maximum summed concentration of PFOA and PFOS was 1.09 μg/L and the median summed value was 0.01 μg/L. Summed PFOA and PFOS concentrations exceeded the EPA HRL (0.07 μg/L) at 1.14% of PWSs (12 PWSs).	Statewide.

In addition to the monitoring data available from public water systems, North Carolina has made data from 17 private wells associated with the Chemours facility in Fayetteville available (NCDEQ, 2018). The maximum combined PFOS and PFOA concentration was 0.0319 μg/L, while the median was 0.004 μg/L. Summed PFOS and PFOA concentrations did not exceed the EPA HRL (0.07 μg/L) at any of the sampling sites. Note that the EPA does not regulate private drinking water wells but may evaluate data from private wells where the data may be indicative of contaminants in aquifers that are used as sources for public water system wells.

UCMR 3 data have also been used by researchers to evaluate co-occurrence of PFAS in drinking water at PWSs. For example, Guelfo and Adamson (2018) investigated PFAS data from UCMR 3 for occurrence and co-contaminant mixtures, trends in PFAS detections relative to PWS characteristics and potential release types, and temporal trends in PFAS occurrence. The study identified that approximately 50% of samples with PFAS detections contained ≥2 PFASs, and 72% of detections occurred in groundwater. Large PWSs (>10,000 customers) were 5.6 times more likely than small PWSs (≤10,000 customers) to exhibit PFAS detections; however, when detected, median total PFAS concentrations were higher in small PWSs (0.12 μg/L) than in large (0.053 μg/L). Hu et al. (2016) presented spatial analysis of PFAS concentrations under UCMR 3 and found that the number of industrial sites

[23] Examples include Chemours Washington Works Facility, West Virginia (production facilities), Horsham Air National Guard Station, Pennsylvania and former Wurtsmith Air Force Base, Michigan (active and former military bases), and non-military firefighting activities (other point sources).

[24] Some of these data in these tables are from targeted sampling efforts and therefore, would be expected to have higher detection rates than a random sample.

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that manufacture or use these compounds, the number of military fire training areas, and the number of wastewater treatment plants are all significant predictors of PFAS detection frequencies and concentrations in public water supplies. The authors found that for PFAS monitored under UCMR 3, the detection frequency in drinking water sourced from groundwater was more than twice that from surface water. Additionally, PFOA and PFOS were more frequently detected in groundwater whereas UCMR 3 PFAS compounds with shorter chain lengths were detected more frequently in surface waters. Hu et al. (2016) noted that this observation could be due to the original mode of environmental release (aerosol, application to soil, and aqueous discharge).

The state data (as presented above and discussed in the Regulatory Determination 4 Support Document), while some are from targeted sampling efforts and therefore, would be expected to have higher detection rates than a random sample, show occurrence in multiple geographic locations consistent with what was observed during UCMR 3 monitoring. Additionally, some state monitoring efforts show detections above the EPA Health Advisory in water systems that were not required to conduct monitoring in the UCMR 3. EPA believes that these data support the Agency's preliminary determination that PFOA and PFOS occur with a frequency and at levels of public health concern in drinking water systems across the United States. Additional details of the EPA analyses of UCMR 3 monitoring data for PFAS can be found in the *Regulatory Determination 4 Support Document* (USEPA, 2019a). The EPA requests comment on whether there are additional occurrence data sets that it can use to supplement the analyses already performed and inform its determination, including more recent data from specific data sets mentioned above.

d. Statutory Criterion #3 (Meaningful Opportunity)

The EPA conducted extensive public outreach in the development of the PFAS Action Plan, including gathering diverse perspectives through the May 2018 National Leadership Summit, direct engagement with the public in impacted communities in five states, engagement with tribal partners, and roundtables conducted with community leaders near impacted sites. In addition, the Agency reviewed approximately 120,000 comments in the public docket that was specifically established to gather input for the Action Plan (USEPA, 2019d). Through these engagements, the EPA heard significant concerns from the public on the challenges these contaminants pose for communities nationwide and the need for uniform, protective drinking water regulations across the United States.

Based on the significant public interest in the potential risks posed by PFOA and PFOS, and the information currently available to the EPA, the Administrator has made the preliminary determination that regulation of PFOA and PFOS presents a meaningful opportunity for health risk reduction for persons served by PWSs. In determining that regulation of PFOA and PFOS presents a meaningful opportunity for health risk reduction for sensitive populations, the EPA was particularly mindful that PFOA and PFOS are known to be transmitted to the fetus via cord blood and to the newborn, infant, and child via breast milk (USEPA, 2016f).

Data from recent state monitoring efforts validate the UCMR 3 monitoring results (USEPA, 2019b; NJ DEP, 2019). Sun et al. observed similar temporal trends in their investigation in the Cape Fear Watershed of North Carolina, where PFAS concentrations remained similar between 2006 and 2013 (Sun et al., 2016). These observations suggest that PFOA and PFOS can be persistent in the environment, lack attenuation processes that would degrade these compounds over time and may be subject to precursor transformations. The EPA believes PFOA and PFOS occur at a frequency and at levels of public health concern. UCMR 3 indicates 1.3% of PWSs (63 PWSs) monitored reported combined PFOA/PFOS above the HRL. These systems serve a total population of approximately 5.6 million people. While this preliminary regulatory determination is based, in part, on the UCMR occurrence data, it is also based on additional factors discussed above.

State data (as described above and discussed in the Regulatory Determination 4 Support Document) support the UCMR results, and the Agency's determination that PFOA and PFOS occur with a frequency and at levels of public health concern in finished drinking water across the United States, with some results substantially elevated above the EPA's HAs. These data have also identified PFAS contamination in other locations, such as in small, previously unmonitored systems, beyond where the UCMR 3 required water systems to conduct monitoring. Due to the anthropogenic nature of PFOA and PFOS and their persistence in the environment, multiple localized areas of contamination across the country may be a significant contributor to drinking water contamination. The state data sets summarized in Table 9 had at least one instance of summed PFOS and PFOA concentrations greater than the HRL of 0.07 μg/L. While many detections are marginally above the EPA HA levels, there are many instances where localized samples substantially exceed the HA levels, sometimes by 2–3 orders of magnitude (*i.e.,* a maximum summed concentration as high as 1.52 μg/L). The EPA believes there is significant public health risk reduction potential in the localized areas with these significantly elevated concentrations. To assess communities with the highest exposures, the ATSDR has begun to perform PFAS exposure assessments in communities near current or former military bases with elevated concentrations of PFAS detected in drinking water (ATSDR, 2019a).

Adverse effects observed following exposures to PFOA and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies (USEPA, 2016g; USEPA, 2016h). States have taken action to reduce exposures (as further discussed below). Some states have established regulatory or guidance levels in drinking water for PFOA, PFOS, as well as other PFAS (ASDWA, 2019). Moving forward with a national-level regulation for PFOA and PFOS may provide additional national consistency and reduce regulatory uncertainty for stakeholders across the country.

PFOA and PFOS are resistant to environmental degradation processes such as hydrolysis, photolysis, and biodegradation and are thus highly persistent in the environment (USEPA, 2019a). In addition, biotic and abiotic processes can degrade PFAS precursors to form PFAAs such as PFOA and PFOS over time and thus are also important contributors to the presence and persistence of these chemicals in the environment (ITRC, 2018). Additionally, PFOA and PFOS are expected to have a high likelihood of partitioning to water based on their ionic nature at typical environmental pH and their organic carbon partitioning coefficients (K_{oc}). PFOA has a high likelihood of partitioning to water based on its water solubility while the water solubility of PFOS anion indicates a moderate likelihood of partitioning to water.

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Therefore, PFOA and PFOS have high mobility and persistence in soil and groundwater and are expected to form larger plumes than less mobile and persistent contaminants in the same hydrogeological setting (ITRC, 2018). In addition, long-range atmospheric transport of PFOA and PFOS through industrial releases (*e.g.,* stack emissions) can accumulate to measurable levels in soils and surface waters away from their point of release (Young et al., 2007; Wallington et al., 2006; Dreyer et al., 2010). Although some manufacturing companies agreed to phase out production of PFOA and PFOS in the United States, other sources could still exist such as fire training and emergency response sites, industrial sites, landfills, and wastewater treatment plant biosolids as well as imported in products (USEPA, 2017c; ITRC, 2018). Drinking water analytical methods are available to measure PFOA, PFOS, and other PFAS in drinking water. The EPA has published validated methodology for detecting a total of 29 unique PFAS in drinking water including EPA Method 537.1 (18 PFAS) (USEPA, 2018b) and EPA Method 533 (25 PFAS) (14 PFAS can be detected by both methods). Therefore, new information about the occurrence of PFAS in drinking water will become available as the Agency further evaluates regulatory action for these contaminants.

Available treatment technologies for removing PFAS from drinking water have been evaluated and reported in the literature (*e.g.,* Dickenson and Higgins, 2016). The EPA's Drinking Water Treatability Database (USEPA, 2019e) summarizes available technical literature on the efficacy of treatment technologies for a range of priority drinking water contaminants, including PFOA and PFOS. Conventional treatment (comprised of the unit processes coagulation, flocculation, clarification, and filtration) is not considered effective for the removal of PFOA. Granular activated carbon (GAC), anion exchange resins, reverse osmosis and nanofiltration are considered effective for the removal of PFOA. However, there are limitations and uncertainties pertaining to these removal processes for PFAS. For example, the treatment efficacy of GAC and anion exchange resins is strongly dependent upon the type of PFAS present and physio-chemical properties of the solution matrix. When mixed PFAS are in the source water, short-chain PFAS will break through the adsorber more quickly. When a system makes treatment technology decisions, it is important to consider the media reactivation and replacement frequency, the cost of reactivation or disposal of spent media, and the potential for overshoot (*i.e.,* higher concentrations of a contaminant in the effluent than the influent, due to preferential adsorption of other contaminants) if a treatment system is operated improperly (Crone et al., 2019; Speth, 2019). Reverse osmosis and nanofiltration are effective for removing a wide range of PFAS. However, they have high capital and operations costs (Crone et al., 2019; Speth, 2019). Additionally, membrane fouling, corrosion control, and the disposal or treatment of concentrate stream are issues that need to be addressed (Crone et al., 2019; Speth, 2019). Additional literature and discussion on the efficacy of these treatments can be found on the EPA's Drinking Water Treatability Database (USEPA, 2019e).

Considering the population exposed to PFOA and PFOS including sensitive populations and lifestages, such as children, the potential adverse human health impacts of these contaminants at low concentrations, the environmental persistence, the persistence in the human body, the availability of both methods to measure and treatment technologies to remove these contaminants, and significant public concerns regarding PFOA and PFOS contamination, the Agency proposes the finding that regulation of PFOA and PFOS presents a meaningful opportunity for health risk reduction for infants, children, and adults, including pregnant and nursing women, served by PWS. While SDWA specifies that the determination of whether PFOA and PFOS present ''a meaningful opportunity for health risk reduction for persons served by public water systems'' is made ''in the sole judgement of the Administrator,'' the EPA seeks public comment on the information and analyses described above.

e. Preliminary Regulatory Determination for PFOA and PFOS

At this stage, the Agency is making a preliminary determination to regulate PFOA and PFOS with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. The EPA has preliminarily determined that PFOA and PFOS may have an adverse effect on human health; that PFOA and PFOS occur in PWSs with a frequency and at levels of public health concern; and that regulation of PFOA and PFOS presents a meaningful opportunity for health risk reduction for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of PFOA and PFOS.

The agency solicits comment on all aspects of this preliminary regulatory determination. In particular, the EPA requests comment on whether there are any additional data the agency should consider in making its final regulatory determination and whether EPA has appropriately considered the data.

f. Considerations for Additional PFAS

As stated in the EPA's PFAS Action Plan (USEPA, 2019d): ''The Agency recognizes that there is additional information that the EPA should evaluate regarding PFAS other than PFOA and PFOS, including new monitoring and occurrence data, recent health effects data, and additional information to be solicited from the public, which will inform the development of a national drinking water regulation for a broader class of PFAS in the future.''

The EPA is aware that many states, tribes, and local communities face challenges from PFAS other than PFOA and PFOS. For example, in addition to PFOA and PFOS, the EPA worked with states and public water systems to characterize the occurrence of four additional PFAS (perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS), perfluoroheptanoic acid (PFHpA), and PFBS)) in the nation's drinking water served by public water systems under UCMR 3. The EPA found that 4.0% of PWSs reported results for which one or more of the six UCMR 3 PFAS were measured at or above their respective MRL. The 4.0% figure is based on 198 PWSs reporting measurable PFAS results for one or more sampling events from one or more of their sampling locations. Those 198 PWS serve an estimated total population of approximately 16 million.

With the voluntary phase-out of PFOA and PFOS, manufacturers are shifting to alternative PFAS compounds (*e.g.,* hexafluoropropylene oxide (HFPO) dimer acid and HFPO dimer acid ammonium salt (GenX chemicals), and perfluorobutanesulfonic acid (PFBS)). There is less publicly available information on the occurrence and health effects of these replacements than for PFOA and PFOS and other members of the carboxylic acid and sulfonate PFAS families (Brendel et al., 2018).

The EPA plans to consider available human health toxicity and occurrence

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information for other PFAS as they become available. The EPA is working on hazard assessments for the following PFAS: GenX chemicals; PFBS; PFNA; perfluorobutanoic acid (PFBA); perfluorodecanoic acid (PFDA); perfluorohexanoic acid (PFHxA); and PFHxS.

The following PFAS have literature available in the EPA's Health and Environmental Research Online (HERO), which is a database of scientific studies and other references used to develop the EPA's risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals. While HERO uses a variety of reference types, the majority are original research published in peer-reviewed literature. For some PFAS, there are epidemiological and/or experimental animal toxicity data available, which may be suitable to inform the evaluation of potential human health effects. Other references provide information on occurrence (both in humans and the environment). Available references for the PFAS listed below can be accessed at: *https://hero.epa.gov/hero/index.cfm/litbrowser/public/#PFAS.*

Chemical name	Acronym	CAS No.
Perfluorooctanoic acid	PFOA	335–67–1
Perfluorooctanesulfonic acid	PFOS	1763–23–1
2H,2H,3H,3H-Perfluorooctanoic acid	5:3 acid	914637–49–3
6:2/8:2 Fluorotelomer phosphate diester	6:2/8:2 diPAP	943913–15–3
Bis[2-(perfluorohexyl)ethyl] phosphate	6:2 diPAP	57677–95–9
Mono[2-(perfluorohexyl)ethyl] phosphate	6:2 monoPAP	57678–01–0
Bis[2-(perfluorooctyl)ethyl] phosphate	8:2 diPAP	678–41–1
Mono[2-(perfluorooctyl)ethyl] phosphate	8:2 monoPAP	57678–03–2
4,8-dioxa-3H-perfluorononanoic acid	ADONA	919005–14–4
6:2 Fluorotelomer alcohol	FtOH 6:2	647–42–7
8:2 Fluorotelomer alcohol	FtOH 8:2	678–39–7
6:2 Fluorotelomer sulfonic acid	FtS 6:2	27619–97–2
8:2 Fluorotelomer sulfonic acid	FtS 8:2	39108–34–4
HFPO dimer acid	GenX chemicals	13252–13–6
HFPO dimer acid ammonium salt	GenX chemicals	62037–80–3
2-(N-Ethylperfluorooctanesulfonamido) acetic acid	NEtFOSAA	2991–50–6
2-(N-Methylperfluorooctanesulfonamido) acetic acid	NMeFOSAA	2355–31–9
Perfluorobutanoic acid	PFBA	375–22–4
Perfluorobutanesulfonic acid	PFBS	375–73–5
Perfluorodecanoic acid	PFDA	335–76–2
Perfluorododecanoic acid	PFDoA	307–55–1
Perfluorodecanesulfonic acid	PFDS	335–77–3
Perfluoroheptanoic acid	PFHpA	375–85–9
Perfluoroheptanesulfonic acid	PFHpS	375–92–8
Perfluorohexanoic acid	PFHxA	307–24–4
Perfluorohexanesulfonic acid	PFHxS	355–46–4
Perfluorononanoic acid	PFNA	375–95–1
Perfluorononanesulfonic acid	PFNS	68259–12–1
Perfluorooctanesulfonamide	PFOSA	754–91–6
Perfluoropentanoic acid	PFPeA	2706–90–3
Perfluoropentanesulfonic acid	PFPeS	2706–91–4
Perfluorotetradecanoic acid	PFTeDA	376–06–7
Perfluoroundecanoic acid	PFUnA	2058–94–8

The EPA continues to work towards filling information gaps for human health, toxicity and occurrence including through collaborations with federal, state, tribal, and other stakeholders. The EPA is generating PFAS toxicology data through new approaches such as high throughput screening, computational toxicology tools, and chemical informatics for chemical prioritization, screening, and risk assessment. This research can inform a more complete understanding of PFAS toxicity for the large set of PFAS chemicals without conventional toxicity data and allow prioritization of actions to potentially address groups of PFAS. For additional information on the new approach methods for PFAS toxicity testing, please visit: *https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions.* To further understand occurrence in drinking water and discussed in the EPA's PFAS Action Plan (USEPA, 2019d), the EPA will propose a nationwide drinking water monitoring for PFAS under the next UCMR monitoring cycle (UCMR 5) utilizing newer methods available to detect more PFAS chemicals and at lower MRLs than previous possible for the earlier UCMR monitoring. These monitoring results will improve understanding of the frequency and concentration of PFAS occurrence in the finished U.S. drinking water.

The EPA is also aware of ongoing toxicity work and guideline development by other federal agencies, state governments, international organizations, industry groups, and other stakeholders. For example, the U.S. National Toxicology Program is conducting ongoing toxicological studies for multiple PFAS compounds of varying length in rats, including 28-day studies for 7 PFAS compounds (3 carboxylates and 4 sulfonates), and a 2-year chronic toxicity and carcinogenicity study for PFOA that is currently undergoing peer-review. ATSDR developed a draft toxicological profile that characterizes toxicologic and adverse health effects information for PFOA, PFOS, and 10 other PFAS compounds which include PFBA, PFHxA, PFHpA, PFNA, PFDA, PFUnA, PFDoA, PFBS, PFHxS, and PFOSA (ATSDR, 2018). Some states, including California, Michigan, Minnesota, New Hampshire, New Jersey, New York and Vermont, are also developing health-based guidance or drinking water standards for individual targeted PFAS or the sum for several targeted PFAS

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(California OEHHA, 2019; Commonwealth of Massachusetts, 2019; MDH, 2019; Michigan Science Advisory Workgroup, 2019; NHDES, 2019; NJDOH, 2017; NYSDOH, 2018; VTDEC, 2019). PFAS that have been or are being evaluated by at least one state include Hexafluoropropylene Oxide (HFPO) Dimer Acid and its Ammonium Salt (GenX chemicals), PFBA, PFBS, PFHpA, PFHxA, PFHxS, PFNA, PFOA, and PFOS. The EPA will evaluate all available and reliable information to inform future decision making for these PFAS contaminants. The EPA is also aware of PFAS monitoring efforts by states and local communities to better understand PFAS occurrence in drinking water, including both statewide drinking water monitoring efforts and targeted sampling at locations that have potentially been impacted by releases or locations where PFAS-containing materials are known to have been used (Table 9). The EPA will consider these other information sources to inform future decisions for other PFAS.

g. Potential Regulatory Approaches

Since PFOA and PFOS raise complicated issues and since the issuance of any NPDWR imposes costs on the public, the EPA is taking advantage of this document by exploring and seeking comment on potential regulatory constructs and monitoring requirements the Agency may consider for PFAS chemicals including PFOA and PFOS if it were to finalize positive regulatory determinations. As noted above in the EPA PFAS Action Plan (USEPA, 2019d), the EPA is seeking information from the public to ''inform the development of national drinking water regulation for a broader class of PFAS in the future''. The EPA is seeking feedback on potential regulatory approaches to address PFAS to support the potential development of a PFOA and PFOS regulation (pending final regulatory determinations) or in future PFAS regulatory actions. The EPA is exploring how to best use the available information when developing potential regulatory approaches for PFAS. Three potential regulatory approach options described below include (1) evaluate each additional PFAS on an individual basis; (2) evaluate additional PFAS by different grouping approaches; and (3) evaluate PFAS based on drinking water treatment techniques.

Evaluate Each Additional PFAS on an Individual Basis

This approach would focus on evaluating PFAS individually for potential future regulatory actions using information completed prior to a potential rule proposal. Examples of suitable information sources the EPA could evaluate under future actions include current and expected peer reviewed toxicity assessments, nationwide drinking water monitoring data, state drinking water monitoring data, and monitoring data from other Federal Agencies. This approach would be limited to those individual PFAS for which sufficient health and occurrence information is available or can be clearly and logically extrapolated. The EPA is actively working to fill information gaps needed to support this approach including developing toxicity assessments for PFBS, HFPO dimer acid and HFPO dimer acid ammonium salt or GenX chemicals, PFBA, PFHxA, PFNA, and PFHxS, and PFDA. The EPA plans to propose nationwide drinking water monitoring for PFAS under the next UCMR monitoring cycle (UCMR 5) utilizing newer methods available to measure more PFAS and at lower minimum reporting levels than previous UCMR monitoring. The EPA may also consider health assessments and occurrence data that are currently being developed by other federal, state and international agencies.

Evaluate Additional PFAS by Different Grouping Approaches

Since the 1940s, over 4000 PFAS have been manufactured and used in a variety of industries across the world (Guelfo et al., 2018; OECD 2019). Evaluations of the retrospective reporting requirements of the TSCA Inventory Notification Rule indicates 602 PFAS are currently commercially active in the United States. The EPA recognizes the challenges associated with evaluating each PFAS that may impact drinking water on an individual basis. The EPA has regulated contaminants as a group in drinking water, including, for example, disinfection byproducts (*i.e.,* haloacetic acids and total trihalomethanes).

In their study of organohalogen flame retardants, the National Academies of Sciences evaluated general approaches to forming chemical classes at regulatory agencies and concluded that a ''science-based class approach does not necessarily require one to evaluate a large chemical group as a single entity for hazard assessment. That is, an approach that divides a large group into smaller units (or subclasses) to conduct the hazard assessment is still a class approach for purposes of hazard or risk assessment'' (NASEM, 2019). An approach to exploring PFAS by groups could, for example, include evaluating groups of PFAS to account for similar physiochemical characteristics. The EPA's ORD and the National Institute of Environmental Health Sciences' (NIEHS) National Toxicology Program recently identified a subset of PFAS for testing with the goals of supporting read-across within structure-based subgroups and capturing the diversity of the broader PFAS class (Helman et al., 2019; Patlewicz et al., 2019a, 2019b). The EPA is also exploring new approaches such as high throughput and computational approaches to explore different chemical categories of PFAS. The EPA will continue research on methods for using these data to support risk assessments using new approach methods such as read-across (*i.e.,* an effort to predict biological activity based on similarity in chemical structure) and transcriptomics (*i.e.,* a measure of changes in gene expression in response to chemical exposure or other external stressors), and to make inferences about the toxicity of PFAS mixtures that commonly occur in real world exposures. Example classifications that the EPA could consider in its group evaluation include common adverse effects, chain length (*e.g.,* long chain and short chain), functional groups (*e.g.,* sulfonates, acids), degradation products (*i.e.,* some PFAS degrade to shorter chain PFAS), co-occurrence, or using a combination of physiochemical and fate characteristics (*e.g.,* long chain perfluoroalkyl sulfonic acids).

Evaluate PFAS Based on Drinking Water Treatment Techniques

SDWA 1412(b)(7)(A) authorizes the EPA to promulgate a treatment technique rule rather than an MCL if the Agency determines it is not economically or technologically feasible to ascertain the level of the contaminant. The EPA continues to develop reliable analytical methods to monitor for PFAS including evaluating methodologies to measure total PFAS. However, the EPA does not anticipate that reliable and validated methods that accurately and precisely capture all PFAS or total PFAS (and not other fluorinated, non-PFAS compounds) will be available for a number of years. Therefore, the Agency is considering whether a treatment technique regulatory approach may be appropriate.

The strength of the carbon-fluorine bond makes certain PFAS (such as perfluoroalkyl acids) relatively stable compounds that are not removed by conventional treatment such as coagulation/flocculation/sedimentation. Technologies that have reported removal efficiencies of greater than 90% for certain PFAS include granulated

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activated carbon, powdered activated carbon, anion exchange resins, nanofiltration and reverse osmosis (Crone et al., 2019; Dickenson and Higgins, 2016; Ross et al., 2018; USEPA, 2019e). Each of these technologies has benefits and limitations that need to be considered if they are to be used when treating PFAS contaminated drinking water, such as cost and operational feasibility (Speth, 2019). For example, nanofiltration and reverse osmosis are highly effective at removing PFAS but are more costly options and generate large waste streams that may require additional treatment. Anion exchange is effective at removing long-chain PFAS constituents but may be less effective at removing short-chain PFAS. Granular activated carbon has the advantage of being a less costly treatment technology and has the ability to be regenerated, however other organic matter present in the influent water may interact and compete for adsorption sites with PFAS, potentially making treatment less effective. In addition, unintended consequences of PFAS treatment also need consideration given regional differences in source water quality and treatment strategies in the United States. Additional discussion on benefits and limitations associated with drinking water treatment technologies for PFAS can be found in the Regulatory Determination Support Document (USEPA, 2019a).

A treatment technique regulation would address multiple PFAS with similar characteristics that may be removed by similar treatment technologies including some for which validated drinking water methods are currently available.

Monitoring Considerations

Should an MCL be established for PFOA, PFOS, and/or other PFAS chemicals pursuant to section 1412 of the SDWA, PWSs could be required to monitor for these contaminants. The EPA may seek to minimize the monitoring burden on water systems while assuring public health protection. Minimizing the monitoring burden to the maximum extent feasible and allowed by statute could reduce costs for drinking water systems that have other important risk-reduction resource demands. The EPA is considering alternative approaches for this monitoring that reduce monitoring frequency for systems that are reliably and consistently below the MCL or do not detect the contaminant. This framework provides primacy agencies with the flexibility to issue monitoring waivers, with the EPA's approval, which take into account regional and state specific characteristics and concerns. The Standardized Monitoring Framework for regulated synthetic organic chemicals under 40 CFR 141.24(h) provides a framework for determining compliance with a potential future MCL. Under this approach, monitoring frequency would be dependent on whether the contaminant has been detected above a certain ''trigger level'' and/or detected above an MCL, and whether a waiver from monitoring has been granted by the Primacy Agency.

An alternative approach to the Standardized Monitoring Framework could be to require monitoring at public water systems only when data show the presence of PFAS in finished drinking water and those designated by the Primacy Agency. Under this approach, monitoring would be required for public water systems with PFAS monitoring data and/or vulnerable systems designated by the state or Primacy Agency. For example, monitoring could be required if a Primacy Agency is aware of information indicating potential PFAS contamination of the public water supply. Information that could be considered includes proximity to facilities with historical or on-going use of fire-fighting foam and proximity to facilities that use or manufacture PFAS.

2. 1,1-Dichloroethane

a. Background

1,1-Dichloroethane is a halogenated alkane. It is an industrial chemical and is used as a solvent and a chemical intermediate. Annual production and importation of 1,1-dichloroethane in the United States was last reported by IUR in 2006 to be between 500,000 and 1 million pounds. The data show that production of 1,1-dichloroethane in the United States has declined since reporting began in 1986. Under CDR, there were no reports of 1,1-dichloroethane production in 2012, 2013, 2014, or 2015 (USEPA, 2019a).

TRI data for 1,1-dichloroethane from the years 1994–2016 show that an average of about 12,000 pounds per year of reported releases have entered the environment from 2003 onward. The number of states with releases of 1,1 dichloroethane has stayed steady at about five since 2004, while the number of states with surface water discharges has averaged two since 1994; surface water discharges ranged from 0 to 235 pounds per year over the approximately 20-year period (USEPA, 2019a).

1,1-Dichloroethane is expected to have a high likelihood of partitioning to water based on its K_{oc} and water solubility. The octanol-water partitioning coefficient (log K_{ow}) indicates that 1,1-dichloroethane is expected to have a moderate likelihood of partitioning to water, while the Henry's Law Constant (K_H) indicates that this compound is expected to have a low likelihood of partitioning to water. 1,1-Dichloroethane is expected to have moderate to high persistence in certain waters based on biodegradation half-lives (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

1,1-Dichloroethane may have an adverse effect on the health of persons. Based on a 13-week gavage study in rats (Muralidhara et al., 2001), the kidney was identified as a sensitive target for 1,1-dichloroethane, and no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 1,000 and 2,000 mg/kg/day, respectively, were identified based on increased urinary enzyme markers for renal damage and central nervous system (CNS) depression (USEPA, 2006a).

The only available reproductive or developmental study with 1,1-dichloroethane is an inhalation study where pregnant rats were exposed on days 6 through 15 of gestation (Schwetz et al., 1974). No effects on the fetuses were noted at 3,800 ppm. Delayed ossification of the sternum without accompanying malformations was reported at a concentration of 6,000 ppm.

A cancer assessment for 1,1-dichloroethane is available on IRIS (USEPA, 1990a). That assessment classifies the chemical, according to the EPA's 1986 *Guidelines for Carcinogenic Risk Assessment* (USEPA, 1986), as Group C, a possible human carcinogen. This classification is based on no human data and limited evidence of carcinogenicity in two animal species (rats and mice), as shown by increased incidences of hemangiosarcomas and mammary gland adenocarcinomas in female rats and hepatocellular carcinomas and benign uterine polyps in mice (NCI, 1978). The data were considered inadequate to support quantitative assessment. The close structural relationship between 1,1-dichloroethane and 1,2-dichloroethane, which is classified as a B2 probable human carcinogen and produces tumors at many of the same sites where marginal tumor increases were observed for 1,1-dichloroethane, supports the suggestion that the 1,1-isomer could possibly be carcinogenic to humans. Mixed results in initiation/promotion studies and genotoxicity assays are

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consistent with this classification. On the other hand, the animals from the 1,1-dichloroethane National Cancer Institute (NCI, 1978) study were housed with animals being exposed to 1,2-dichloroethane providing opportunities for possible co-exposure impacting the 1,1-dichloroethane results. The following groups of individuals may have an increased risk from exposure to 1,1-dichloroethane (NIOSH, 1978; ATSDR, 2015):

- Those with chronic respiratory disease
- Those with liver diseases that impact hepatic microsomal cytochrome P–450 functions
- Individuals with impaired renal function and vulnerable to kidney stones
- Individuals with skin disorders vulnerable to irritation by solvents like 1,1- dichloroethane
- Those who consume alcohol or use pharmaceuticals (*e.g.,* phenobarbital) that alter the activity of cytochrome P–450s

A provisional chronic RfD was derived from the 13-week gavage study in rats based on a NOAEL of 1,000 mg/kg/day administered for five days/week and adjusted to 714.3 mg/kg/day for continuous exposure (an increase in urinary enzymes was the adverse impact on the kidney). The chronic oral RfD of 0.2 mg/kg/day was derived by dividing the normalized NOAEL of 714.3 mg/kg/day in male Sprague-Dawley rats by a combined UF of 3,000. The combined UF includes factors of 10 for interspecies extrapolation, 10 for extrapolation from a subchronic study, 10 for human variability, and 3 for database deficiencies (including lack of reproductive and developmental toxicity tests by the oral route). This assessment noted several limitations in the critical study and database as a whole. Specifically, that the reporting of the results in the critical study were marginally adequate and that the database lacks information on reproductive and developmental and nervous system toxicity.

The EPA calculated an HRL for 1,1-dichloroethane of 1,000 µg/L, based on the EPA oral RfD of 0.2 mg/kg/day, using 2.5 L/day drinking water ingestion, 80 kg body weight and a 20% RSC factor.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that 1,1-dichloroethane does not occur with a frequency and at levels of public health concern in public water systems based on the EPA's evaluation of the following occurrence information.

The primary occurrence data for 1,1-dichloroethane are recent (2013–2015) nationally-representative drinking water monitoring data generated through the EPA's UCMR 3. Under UCMR 3, 36,848 samples were collected from 4,916 PWSs and analyzed for 1,1-dichloroethane. The contaminant was not detected in any of the samples at levels greater than ½ the HRL (500 µg/L) or the HRL (1,000 µg/L). 1,1-Dichloroethane was detected in about 2.3% samples at or above the MRL (0.03 µg/L) (USEPA, 2019a; USEPA, 2019b).

Occurrence data for 1,1-dichloroethane in finished drinking water are also available from UCM Rounds 1 and 2 (1988–1992 and 1993–1997). None of those samples exceeded ½ the HRL or the HRL. In the Round 1 cross-section states, 1,1 dichloroethane was detected at 233 PWSs (1.14% of PWSs). Detected concentrations ranged from 0.01 µg/L to 500 µg/L. In the Round 2 cross-section states, 1,1 dichloroethane was detected at 184 PWSs (0.74% of PWSs). Detected concentrations ranged from 0.00126 µg/L to 159 µg/L (USEPA, 2008c; USEPA, 2019a).

Occurrence data for 1,1-dichloroethane in ambient water are available from the NAWQA program. Those data show that 1,1-dichloroethane was detected in between 2% and 4% of samples from between 2% and 4% of sites. No detections were greater than the HRL. The median concentrations based on detections were less than 0.06 µg/L (WQP, 2018). Ambient water data for 1,1-dichloroethane analysis are also available from the NWIS database. Those data show that 1,1-dichloroethane was detected in approximately 5% of samples (1,152 out of 24,560) and at approximately 5% of sites (620 out of 12,057). The median concentration of detections was 0.380 µg/L (USEPA, 2019a).

d. Statutory Criterion #3 (Meaningful Opportunity)

1,1-Dichloroethane does not present a meaningful opportunity for health risk reduction through regulation for persons served by PWSs based on the estimated exposed population, including sensitive populations. UCMR 3 findings indicate that the estimated population exposed to 1,1-dichloroethane at levels of public health concern is 0%. As a result, the Agency finds that an NPDWR for 1,1-dichloroethane does not present a meaningful opportunity for health risk reduction.

e. Preliminary Regulatory Determination for 1,1-dichloroethane

The Agency is making a preliminary determination to not regulate 1,1-dichloroethane with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that 1,1-dichloroethane may have an adverse effect on human health, the occurrence data indicate that 1,1-dichloroethane is not occurring or is not likely to occur in PWSs with a frequency and at levels of public health concern. Therefore, the Agency has determined that an NPDWR for 1,1-dichloroethane would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of 1,1-dichloroethane.

3. Acetochlor

a. Background

Acetochlor is a chloroacetanilide pesticide that is used as an herbicide for pre-emergence control of weeds. It was first registered by the EPA in 1994. It is registered for use on corn crops (field corn and popcorn); corn fields treated with acetochlor may later be rotated to grain sorghum (milo), soybeans, wheat, and tobacco. In March of 2006, the EPA released a *Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Acetochlor* (USEPA, 2006b). In 2010, the EPA approved the use of acetochlor on cotton as a rotational crop (USEPA, 2010a). Synonyms for acetochlor include 2-chloro-2′-methyl-6-ethyl-N-ethoxymethylacetanilide (USEPA, 2019a).

According to the EPA Pesticide Industry Sales and Usage reports, the amount of acetochlor active ingredient used in the United States was between 31 and 36 million pounds in 1997; between 30 and 35 million pounds in 1999, 2001 and 2003; between 26 and 31 million pounds in 2005; between 28 and 33 million pounds in 2007; between 23 and 33 million pounds in 2009; and between 28 and 38 million pounds in 2012 (USEPA, 2019a).

USGS pesticide use data show that there has been an increase in the annual usage of acetochlor, from about 32 million pounds per year in 2010 to over 45 million pounds in 2016. This increase can largely be attributed to the

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use of acetochlor on crops other than corn (USEPA, 2019a).

If released to soil, acetochlor is expected to have moderate to high mobility (HSDB, 2012). Acetochlor is expected to have a high likelihood of partitioning to water based on its K_H. The values for K_{oc} indicate that acetochlor is expected to have a moderate to high likelihood of partitioning to water. The water solubility indicates that acetochlor is expected to have a moderate likelihood of partitioning to water. Acetochlor is expected to have low to moderate persistence based on aerobic and anaerobic biodegradation/biotransformation half-lives (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

Acetochlor may have an adverse effect on the health of persons. Subchronic and chronic oral studies have demonstrated adverse effects on the liver, thyroid (secondary to the liver effects), nervous system, kidney, lung, testes, and erythrocytes in rats and mice (USEPA, 2006c; USEPA, 2018c). There was evidence of carcinogenicity in studies conducted with acetochlor in rats and mice and a non-mutagenic mode of action was demonstrated for nasal and thyroid tumors in rats (USEPA, 2006c). Cancer effects include nasal tumors and thyroid tumors in rats, lung tumors and histocytic sarcomas in mice, and liver tumors in both rats and mice (Ahmed and Seely, 1983; Ahmed et al., 1983; Amyes, 1989; Hardisty, 1997a; Hardisty, 1997b; Hardisty, 1997c; Naylor and Ribelin, 1986; Ribelin, 1987; USEPA, 2004b; USEPA, 2006c; and Virgo and Broadmeadow, 1988). No biologically sensitive human subpopulations have been identified for acetochlor. Developmental and reproductive toxicity studies do not indicate increased susceptibility to acetochlor exposure at early life stages in test animals (USEPA, 2006c).

The study used to derive the oral RfD is a 1-year oral chronic feeding study conducted in beagle dogs. This study describes a NOAEL of 2 mg/kg/day, and a LOAEL of 10 mg/kg/day, based on the critical effects of increased salivation; increased levels of alanine aminotransferase (ALT) and ornithine carbamoyl transferase (OTC); increased triglyceride levels; decreased blood glucose levels; and alterations in the histopathology of the testes, kidneys, and liver of male beagle dogs (USEPA, 2018c; ICI, Inc., 1988). The UF applied was 100 (10 for intraspecies variation and 10 for interspecies extrapolation). The EPA OPP RfD for acetochlor of 0.02 mg/kg/day, based on the NOAEL of 2 mg/kg/day from the 1-year oral chronic feeding study in beagle dogs, is expected to be protective of both noncancer and cancer effects.

The EPA calculated an HRL of 100 µg/L based on the EPA OPP RfD for non-cancer effects for acetochlor of 0.02 mg/kg/day (USEPA, 2018c) using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 20% RSC factor.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that acetochlor does not occur with a frequency and at levels of public health concern in public water systems based on the EPA's evaluation of the following occurrence information.

The primary data for acetochlor are from the UCMR 1 a.m. (2001–2003) and UCMR 2 SS (2008–2010). Acetochlor was not detected at or above the MRL of 2 µg/L or above the HRL of 100 µg/L in any of the 33,778 UCMR 1 a.m. samples (USEPA, 2008b; USEPA, 2019a) or in any of the 11,193 UCMR 2 SS samples (USEPA, 2015a; USEPA, 2019a).

To ascertain the impact of increased usage of acetochlor since the end of UCMR 2, the EPA assessed ambient water and limited finished water data collected after 2010. Sources of such data include the NAWQA program and the NWIS database. Three cycles of NAWQA data show that acetochlor was detected in between 13% and 23% of samples from between 3% and 10% of sites. While maximum values in NAWQA Cycle 2 (2002–2012) and Cycle 3 (2013–2017) monitoring exceeded the HRL (215 µg/L in 2004 and 137 µg/L in 2013) (only one sample in each of those two cycles exceeded the HRL), 90th percentile levels of acetochlor remained below 1 µg/L. More than 10,000 samples were collected in each cycle. Non-NAWQA NWIS data (1991–2016), which included limited finished water data in addition to the ambient water data, show no detected concentrations greater than the HRL (USEPA, 2019a).

d. Statutory Criterion #3 (Meaningful Opportunity)

Acetochlor does not present a meaningful opportunity for health risk reduction for persons served by PWSs based on the estimated exposed population, including sensitive populations. The estimated population exposed to acetochlor at levels of public health concern is 0% based on UCMR 1 finished water data gathered from 2001 to 2003 and UCMR 2 finished water data gathered from 2008 to 2010. As a result, the Agency finds that an NPDWR for acetochlor does not present a meaningful opportunity for health risk reduction.

e. Preliminary Regulatory Determination for Acetochlor

The Agency is making a preliminary determination to not regulate acetochlor with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that acetochlor may have an adverse effect on human health, the occurrence data indicate that acetochlor is not occurring or not likely to occur in PWSs with a frequency and at levels of public health concern. The EPA also noted that the use of acetochlor has increased since the nationally representative data collection from finished water under UCMR 2 (*i.e.,* 2008–2010). A review of ambient and limited finished water monitoring data collected since 2010 in NAWQA and NWIS show no 90th percentile values exceeding 1 µg/L.

Therefore, the Agency has determined that an NPDWR for acetochlor would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a), *The Analysis of Occurrence Data from the First Unregulated Contaminant Monitoring Regulation (UCMR 1) in Support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List* (USEPA, 2008b), and the *Occurrence Data from the Second Unregulated Contaminant Monitoring Regulation (UCMR 2)* (USEPA, 2015a) present additional information and analyses supporting the Agency's evaluation of acetochlor.

4. Methyl Bromide (Bromomethane)

a. Background

Methyl bromide is a halogenated alkane and occurs as a gas. Methyl bromide has been used as a fumigant fungicide, applied to soil before planting, to crops after harvest, to vehicles and buildings, and for other specialized purposes.

Methyl bromide is an ozone-depleting chemical regulated under the Montreal Protocol. Use of the chemical in the United States was phased out in 2005, except for specific critical use exemptions and quarantine and pre-shipment exemptions. Critical use exemptions have included strawberry cultivation and production of dry cured pork. Additional information on the methyl bromide phase-out and exemptions in the United States can be found on the EPA's website: *https://*

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www.epa.gov/ods-phaseout/methyl-bromide.

In August of 2006, the EPA released a TRED for methyl bromide and a RED for commodity uses (USEPA, 2006d). A RED for soil fumigant uses was released in July 2008, and amended in May 2009 (USEPA, 2009e). In 2011, the EPA issued a cancellation order for certain soil-related uses of methyl bromide, but this order did not affect its use as a post-harvest fumigant (76 FR 29238; USEPA, 2011d). Synonyms for methyl bromide include bromomethane, monobromomethane, curafume, Meth-O-Gas, and Brom-O-Sol (HSDB, 2019).

A report by the United Nations Environment Programme (UNEP, 2018) indicates that critical use exemptions in the United States under the Montreal Protocol declined steadily from 9,553 metric tons of methyl bromide in 2005 to 235 metric tons in 2016 and stood at 0 in 2017 and 2018. A total 50 metric tons were ''on hand'' in the United States at the end of 2016 (UNEP, 2018). Exempted quarantine and pre-shipment uses continue. Production data for methyl bromide are available from the EPA's IUR and CDR programs, and industrial release data are available from the EPA's TRI database, as described below.

The most recent quantities of methyl bromide produced and imported (in 2013, 2014, and 2015, as reported in CDR) are classified as CBI. The last publicly available data for production of methyl bromide are from 2006, under IUR, when production was in the range of 10 to <50 million pounds (USEPA, 2019a).

TRI data from 1988 to 2016 show a general long-term declining trend in industrial releases of methyl bromide, from over one million pounds per year in the 1990s to under 500,000 pounds most years since 2010. Air emissions have tended to dominate releases, with the exception of 2015, when an anomalous large quantity (350,000 pounds) was reported released by underground injection from a single facility. In 2016, facilities in 11 states reported releases of any kind and facilities in two states reported on-site surface water discharges (USEPA, 2019a).

According to the EPA's Pesticide Industry Sales and Usage reports, the amount of methyl bromide active ingredient used in the United States was between 38 and 45 million pounds in 1997; between 28 and 33 million pounds in 1999; between 20 and 25 million pounds in 2001; between 13 and 17 million pounds in 2003; between 12 and 16 million pounds in 2005; between 11 and 15 million pounds in 2007; between 5 and 9 million pounds in 2009; and between 2 and 6 million pounds in 2012 (USEPA, 2019a).

USGS pesticide use data show that there has been a decrease of methyl bromide use through 2016 down to about 2 million pounds from a high of about 78 million pounds in 1995 (USGS, 2018).

If released to dry or moist soil, methyl bromide is expected to be volatile (HSDB, 2019); its K_H indicates that methyl bromide is expected to have a low likelihood of partitioning to water from air. Methyl bromide is expected to have a high likelihood of partitioning to water based on its K_{oc} and water solubility. The log K_{ow} indicates that methyl bromide is expected to have a moderate likelihood of partitioning to water. Methyl bromide is predicted to have low persistence in soil based on experiments under simulated conditions in reaction with aniline. Measured hydrolysis half-lives indicate moderate persistence in water (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

Methyl bromide may have an adverse effect on the health of persons. The limited number of studies investigating the oral toxicity of methyl bromide indicate that the route of administration influences the toxic effects observed (USEPA, 2006e). The forestomach of rats (forestomachs are not present in humans) appears to be the most sensitive target of methyl bromide when it is administered orally by gavage (ATSDR, 1992a). Acute and subchronic oral gavage studies in rats identified stomach lesions (Kaneda et al., 1998), hyperemia (excess blood) (Danse et al., 1984), and ulceration (Boorman et al., 1986; Danse et al., 1984) of the forestomach. However, forestomach effects were not observed in rats and stomach effects were not observed in dogs that were chronically exposed to methyl bromide in the diet, potentially because methyl bromide degrades to other bromide compounds in the food (Mertens, 1997). Decreases in food consumption, body weight, and body weight gain were noted in the chronic rat study when methyl bromide was administered in capsules (Mertens, 1997).

In a subchronic (13-week) rat study (Danse et al., 1984), a NOAEL of 1.4 mg/kg/day (a time weighted average, 5/7 days, of the 2 mg/kg/day dose group) was selected in the EPA IRIS assessment based on severe hyperplasia of the stratified squamous epithelium in the forestomach, in the next highest dose group of 7.1 mg/kg/day (USEPA, 1989a). In ATSDR's Toxicological Profile (ATSDR, 1992a), a lower dose of 0.4 mg/kg/day is selected as the NOAEL because ''mild focal hyperemia'' was observed at the 1.4 mg/kg/day dose level. It is worth noting that authors of this study reported neoplastic changes in the forestomach. However, the EPA and others (USEPA, 1985; Schatzow, 1984) re-evaluated the histological results, concluding that the lesions were hyperplasia and inflammation, not neoplasms. ATSDR notes that histological diagnosis of epithelial carcinomas in the presence of marked hyperplasia is difficult (Wester and Kroes 1988; ATSDR 1992a). Additionally, the hyperplasia of the forestomach observed after 13 weeks of exposure to bromomethane regressed when exposure ended (Boorman et al. 1986; ATSDR 1992a).

The EPA selected an OPP Human Health Risk Assessment from 2006 as the basis for developing the HRL for methyl bromide (USEPA, 2006e). As described in the OPP document, the study was of chronic duration (two years) with four groups of male rats and four groups of female rats treated orally via encapsulated methyl bromide. In the OPP assessment (USEPA, 2006e), Mertens (1997) was identified as the critical study and decreased body weight, decreased rate of body weight gain, and decreased food consumption were the critical effects in rats orally exposed to methyl bromide (USEPA, 2006e). The NOAEL was 2.2 mg/kg/day and the LOAEL was 11.1 mg/kg/day. The RfD derived in the 2006 OPP Human Health Assessment is 0.022 mg/kg/day, based on the point of departure (POD) of 2.2 mg/kg/day (the NOAEL) and a combined uncertainty factor (UF) of 100 for interspecies variability (10) and intraspecies variability (10). No benchmark dose modeling was performed.

Neurological effects reported after inhalation exposures have not been reported after oral exposures, indicating that route of exposure may influence the most sensitive adverse health endpoint (USEPA, 1988).

Limited data are available regarding the developmental or reproductive toxicity of methyl bromide, especially via the oral route of exposure. ATSDR (1992a) found no information on developmental effects in humans with methyl bromide exposure. An oral developmental toxicity study of methyl bromide in rats (doses of 3, 10, or 30 mg/kg/day) and rabbits (doses of 1, 3, or 10 mg/kg/day) found that there were no treatment-related adverse effects in fetuses of the treated groups of either species (Kaneda et al., 1998). ATSDR's 1992 Toxicological Profile also did not

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identify any LOAELs for rats or rabbits in this study. In rats exposed to 30 mg/kg/day, there was an increase in fetuses having 25 presacral vertebrae; however, ATSDR notes that there were no significant differences in the number of litters with this variation and the effect was not exposure-related (ATSDR, 1992a). No significant alterations in resorptions or fetal deaths, number of live fetuses, sex ratio, or fetal body weights were observed in rats and no alterations in the occurrence of external, visceral, or skeletal malformations or variations were observed in the rabbits. Some inhalation studies reported no effects on development or reproduction, but other inhalation studies show adverse developmental effects. For example, Hardin et al. (1981) and Sikov et al. (1980) conducted studies in rats and rabbits and found no developmental effects, even when maternal toxicity was severe (ATSDR, 1992a). However, another inhalation study of rabbits found increased incidence of gallbladder agenesis, fused vertebrae, and decreased fetal body weights in offspring (Breslin et al., 1990). Decreased pup weights were noted in a multigeneration study in rats exposed to 30 ppm (Enloe et al., 1986). Reproductive effects were noted in intermediate-duration inhalation studies in rats and mice (Eustis et al., 1988; Kato et al., 1986), which indicated that the testes may undergo degeneration and atrophy at high exposure levels.

In the OPP HHRA for methyl bromide (USEPA, 2006e), methyl bromide is classified as ''not likely to be carcinogenic to humans''. In 2007, the EPA published a PPRTV report which stated that there is ''inadequate information to assess the carcinogenic potential'' of methyl bromide in humans (USEPA, 2007b). The PPRTV assessment agrees with earlier National Toxicology Program (NTP) conclusions that the available data indicate that methyl bromide can cause genotoxic and/or mutagenic changes. The PPRTV assessment states that the results in studies by Vogel and Nivard (1994) and Gansewendt et al. (1991) clearly indicate methyl bromide is distributed throughout the body and is capable of methylating DNA in vivo. However, the PPRTV assessment also summarizes the results of several studies in mice and rats that have not demonstrated evidence of methyl bromide-induced carcinogenic changes (USEPA, 2007b; NTP, 1992; Reuzel et al. 1987; ATSDR, 1992a). In 2012, an epidemiology study was published that concluded there was a significant monotonic exposure-dependent increase in stomach cancer risk among 7,814 applicators of methyl bromide (Barry et al., 2012). In OPP's Draft HHRA for Methyl Bromide, OPP reviews all the epidemiological studies for methyl bromide, including the Barry et al. (2012) Agricultural Health Study. OPP concludes that ''based on the review of these studies, there is insufficient evidence to suggest a clear associative or causal relationship between exposure to methyl bromide and carcinogenic or non-carcinogenic health outcomes.''

According to ATSDR (1992a) and the EPA OPP assessment (USEPA, 2006e), no studies suggest that a specific subpopulation may be more susceptible to methyl bromide, though there is little information about susceptible lifestages or subpopulations when exposed via the oral route. Because the critical effects of decreased body weight, decreased rate of body weight gain, and decreased food consumption in this study are not specific to a sensitive subpopulation or life stage, the target population of the general adult population was selected in deriving the HRL for regulatory determination. EPA's OPP assessment conducted additional exposure assessments for lifestages that may increase exposure to methyl bromide and concluded that no lifestages have expected exposure greater than 10% of the chronic population-adjusted dose (cPAD), including children.

The EPA calculated an HRL of 100 µg/L (rounded from 140.8 µg/L) based on an EPA OPP assessment cPAD of 0.022 mg/kg/day and using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 20% RSC factor (USEPA, 2006d; USEPA, 2011b, Table 8–1 and 3–33).

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that methyl bromide does not occur with a frequency and at levels of public health concern in PWSs based on the EPA's evaluation of the following occurrence information.

The primary data for methyl bromide are from the UCMR 3 a.m., which was collected from January 2013 to December 2015. A total of 36,848 samples for methyl bromide were collected from 4,916 systems. Of these systems, 49 (1.0% of systems) reported at least one detection at or above the MRL of 0.2 µg/L. A total of 0.31% of samples had concentrations greater than or equal to the MRL (0.2 µg/L). Reported methyl bromide concentrations range from 0.2 µg/L to 6.9 µg/L. There was no occurrence above the ½ HRL or HRL thresholds.

In all three NAWQA cycles, methyl bromide was detected in fewer than 1% of samples from fewer than 2% of sites. No detections were greater than the HRL in any of the three cycles. The median concentration among detections were 0.5 µg/L and 0.8 µg/L in Cycle 1 and Cycle 3, respectively. There were no detections in Cycle 2. The results of the non-NAWQA NWIS analysis show that methyl bromide was detected in approximately 0.1% of samples at approximately 0.1% of sites. The median concentration among detections was 0.6 µg/L.

d. Statutory Criterion #3 (Meaningful Opportunity)

Methyl bromide does not present a meaningful opportunity for health risk reduction for persons served by PWSs based on the estimated exposed population, including sensitive populations. UCMR 3 findings indicate that the estimated population exposed to methyl bromide at levels of public health concern is 0%. As a result, the Agency finds that an NPDWR for methyl bromide does not present a meaningful opportunity for health risk reduction.

e. Preliminary Regulatory Determination for Methyl Bromide

The Agency is making a preliminary determination to not regulate methyl bromide with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that methyl bromide may have an adverse effect on human health, the occurrence data indicate that methyl bromide is not occurring or not likely to occur in PWSs with a frequency and at levels of public health concern. Furthermore, in accordance with U.S. obligations under the Montreal Protocol, production and importation of methyl bromide has steadily declined since 2005.

Therefore, the Agency has determined that an NPDWR for methyl bromide would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of methyl bromide.

5. Metolachlor

a. Background

Metolachlor is a chloroacetanilide pesticide that is used as an herbicide for weed control. Initially registered in

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1976 for use on turf, metolachlor has more recently been used on corn, cotton, peanuts, pod crops, potatoes, safflower, sorghum, soybeans, stone fruits, tree nuts, non-bearing citrus, non-bearing grapes, cabbage, certain peppers, buffalograss, guymon bermudagrass for seed production, nurseries, hedgerows/fencerows, and landscape plantings. In April of 1995, the EPA released a RED for metolachlor (USEPA, 1995b) and a TRED was released in June of 2002 (USEPA, 2002c). In 2012, the EPA reinstated tolerances for metolachlor on popcorn to rectify an omission of these tolerances in previous documentation (USEPA, 2012b). The metolachlor molecule can exist in right- and left-handed versions (enantiomers), labeled ''R-'' and ''S-''. (The chemical terms are dextrorotatory and levorotatory: the factor refers to the direction the compound in solution rotates polarized light.) The ''S-'' version is more potent as a pesticide. When manufacturers found a way of producing metolachlor that was predominantly the ''S-'' enantiomer in the late 1990s, they began marketing that as ''S-metolachlor,'' while the racemic (roughly evenly balanced) mixture continues to be sold as ''metolachlor'' (Hartzler, 2004). Metolachlor and S-metolachlor are under registration review (USEPA, 2014b). Synonyms for metolachlor include dual and bicep (USEPA, 2019a).

Based on private market usage data, the EPA estimated that approximately 9 million pounds of metolachlor active ingredient and 28 million pounds of S-metolachlor active ingredient were applied annually between 1998 and 2012, both mostly on corn (USEPA, 2014b).

According to the EPA's Pesticide Industry Sales and Usage reports, the amount of metolachlor active ingredient (the racemic mixture) used in the United States was between 45 and 50 million pounds in 1987; between 63 and 69 million pounds in 1997; between 26 and 30 million pounds in 1999; between 15 and 22 million pounds in 2001; between 1 and 5 million pounds on 2009; and between 4 and 8 million pounds in 2012. Furthermore, the amount of S-metolachlor active ingredient used was between 16 and 19 million pounds in 1999; between 20 and 24 million pounds in 2001; between 28 and 33 million pounds in 2003; between 27 and 32 million pounds in 2005; between 30 and 35 million pounds in 2007; between 24 and 34 million pounds in 2009; and between 34 and 44 million pounds in 2012 (USEPA, 2019a).

USGS pesticide use data show that there has been a mild increase in metolachlor (racemic mixture) with a greater change in the amount of S-metolachlor relative to metolachlor. Between 2010 and 2016, the increase in metolachlor usage is about 3 million pounds, or about 30%, and for S-metolachlor the increase is about 25 million pounds, or about 75% (USEPA, 2019a).

If released to soil, metolachlor is expected to have moderate to high mobility. The EPA's RED document indicates that substantial leaching and/or runoff of metolachlor from soil is expected to occur (USEPA, 1995b). Metolachlor is expected to have a high likelihood of partitioning to water based on its $K_{H,}$ while its log K_{ow} and water solubility indicate that metolachlor is expected to have a moderate likelihood of partitioning to water. The literature provides a wide range of values for K_{oc} (USEPA, 2019a provides additional information). Metolachlor is expected to have moderate to high persistence in soil and water under aerobic conditions based on aerobic biodegradation half-lives and high persistence in soil and water under anaerobic conditions based on anaerobic biodegradation half-lives (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

Metolachlor may have an adverse effect on the health of persons. The existing toxicological database includes studies evaluating both metolachlor and S-metolachlor. When combined with the toxicology database for metolachlor, the toxicology database for S-metolachlor is considered complete for risk assessment purposes (USEPA, 2018d). In subchronic (metolachlor and S-metolachlor) (USEPA, 1995b; USEPA, 2018d) and chronic (metolachlor) (Hazelette, 1989; Tisdel, 1983; Page, 1981; USEPA, 2018d) toxicity studies in dogs and rats, decreased body weight was the most commonly observed effect. Chronic exposure to metolachlor in rats also resulted in increased liver weight and microscopic liver lesions in both sexes (USEPA, 2018d). No systemic toxicity was observed in rabbits when metolachlor was administered dermally, though dermal irritation was observed at lower doses (USEPA, 2018d). Portal of entry effects (*e.g.,* hyperplasia of the squamous epithelium and mucous cell) occurred in the nasal cavity at lower doses in a 28-day inhalation study in rats (USEPA, 2018d). Systemic toxicity effects were not observed in this study. Immunotoxicity effects were not observed in mice exposed to S-metolachlor (USEPA, 2018d).

While some prenatal developmental studies in the rat and rabbit with both metolachlor and S-metolachlor revealed no evidence of a qualitative or quantitative susceptibility in fetal animals, decreased pup body weight was observed in a two-generation study (Page, 1981, USEPA, 2018d). Though there was no evidence of maternal toxicity, decreased pup body weight in the F1 and F2 litters was observed, indicating developmental toxicity (Page, 1981; USEPA, 1990b). Therefore, sensitive lifestages to consider include infants, as well as pregnant women and their fetus, and lactating women.

Although treatment with metolachlor did not result in an increase in treatment-related tumors in male rats or in mice (both sexes), metolachlor caused an increase in liver tumors in female rats (USEPA, 2018d). There was no evidence of mutagenic or cytogenetic effects in vivo or in vitro (USEPA, 2018d). In 1994 (USEPA, 1995b), the EPA classified metolachlor as a Group C possible human carcinogen, in accordance with the 1986 *Guidelines for Carcinogen Risk Assessment* (USEPA, 1986). In 2017 (USEPA, 2018d), the EPA re-assessed the cancer classification for metolachlor in accordance with the EPA's final *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005b), and reclassified metolachlor/S-metolachlor as ''Not Likely to be Carcinogenic to Humans'' at doses that do not induce cellular proliferation in the liver. This classification was based on convincing evidence of a constitutive androstane receptor (CAR)-mediated mitogenic MOA for liver tumors in female rats that supports a nonlinear approach when deriving a guideline that is protective for the tumor endpoint (USEPA, 2018d).

A recent OPP HHRA identified a two-generation reproduction study in rats as the critical study (USEPA, 2018d). OPP proposed an RfD for metolachlor of 0.26 mg/kg/day, derived from a NOAEL of 26 mg/kg/day for decreased pup body weight in the F1 and F2 litters. A combined UF of 100 was used based on interspecies extrapolation (10), intraspecies variation (10), and an FQPA Safety Factor of 1.[24] This RfD is

[24] The EPA notes that for pesticide registrations under FIFRA, EPA's Office of Pesticides derives acute or chronic population adjusted doses (PADs) using an FQPA Safety Factor mandated by the FQPA taking into consideration potential pre and/or postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. In the majority of instances, the PAD and the RfD are the same. It is only in those few instances when the FQPA Safety Factor is attributed to residual uncertainty with regard to exposure or pre/postnatal toxicity that the RfD and PAD differ. More recently, FQPA Safety Factors can account for uncertainties in the overall completeness of the

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considered protective of carcinogenic effects as well as effects observed in chronic toxicity studies (USEPA, 2018d). The decreased F1 and F2 litter pup body weights in the absence of maternal toxicity were considered indicative of increased susceptibility to the pups. Therefore, a rate of 0.15 L/kg/day was selected from the *Exposure Factors Handbook* (USEPA, 2011b) to represent the consumers-only estimate of DWI based on the combined direct and indirect community water ingestion at the 90th percentile for bottle fed infants. This estimate is more protective than the estimate for pregnant women (0.033 L/kg/day) or lactating women (0.054 L/kg/day). DWI and BW parameters are further outlined in the *Exposure Factors Handbook* (USEPA, 2011b).

The EPA OW calculated an HRL for metolachlor of 300 µg/L (rounded from 0.347 mg/L). The HRL was derived from the oral RfD of 0.26 mg/kg/day for bottle fed infants ingesting 0.15 L/kg/day water, with the application of a 20% RSC.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that metolachlor does not occur with a frequency and at levels of public health concern in public water systems based on the EPA's evaluation of the following occurrence information.

The primary data for metolachlor are from the UCMR 2 SS. A total of 11,192 metolachlor samples were collected from 1,198 systems. Of these systems, three (0.25%) had metolachlor detections and none of the detections were greater than ½ the HRL or the HRL of 300 µg/L (USEPA, 2015a; USEPA, 2019a).

Nationally representative finished water occurrence data for metolachlor are also available from the UCM Round 2 data set. In the Round 2 cross-section states, metolachlor was detected at 108 PWSs (0.83% of PWSs). Detected concentrations ranged from 0.01 µg/L to 13.8 µg/L. There were no exceedances of ½ the HRL or the HRL of 300 µg/L (USEPA, 2008c; USEPA, 2019a).

To ascertain the impact of increased usage of metolachlor since the end of UCMR 2, the EPA assessed ambient water and limited finished water data collected after 2010. Sources of such data include the NAWQA program and the NWIS database. The EPA found no values in the NAWQA data set that exceeded the HRL. The highest value in the NWIS data set (376 µg/L) exceeded the HRL, but the 99th percentile value (13.3 µg/L) did not exceed the HRL[25] (USEPA, 2019a).

d. Statutory Criterion #3 (Meaningful Opportunity)

Metolachlor does not present a meaningful opportunity for health risk reduction for persons served by PWSs based on the estimated exposed population, including sensitive populations. UCMR 2 findings indicate that the estimated population exposed to metolachlor at levels of public health concern is 0%. As a result, the Agency finds that an NPDWR for metolachlor does not present a meaningful opportunity for health risk reduction.

e. Preliminary Regulatory Determination for Metolachlor

The Agency is making a preliminary determination to not regulate metolachlor with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that metolachlor may have an adverse effect on human health, the occurrence data indicate that metolachlor is not occurring or not likely to occur in PWSs with a frequency and at levels of public health concern. The EPA will continue to evaluate metolachlor as new finished water data become available.

Therefore, the Agency has determined that an NPDWR for metolachlor would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Second Unregulated Contaminant Monitoring Regulation (UCMR 2)* (USEPA, 2015a) present additional information and analyses supporting the Agency's evaluation of metolachlor.

6. Nitrobenzene

a. Background

Nitrobenzene is a synthetic aromatic nitro compound and occurs as an oily, flammable liquid. It is commonly used as a chemical intermediate in the production of aniline and drugs such as acetaminophen. Nitrobenzene is also used in the manufacturing of paints, shoe polishes, floor polishes, metal polishes, aniline dyes, and pesticides (USEPA, 2019a).

IUR data indicate that production of nitrobenzene in the United States increased between 1986 and 1990 and stood at over 1 billion pounds per year from 1990 to 2006. Data from the EPA's CDR program indicate that production of nitrobenzene was in the range of 1–5 billion pounds per year in 2012, 2013, 2014, and 2015 (USEPA, 2019a).

TRI data for nitrobenzene show that total releases were in the range of hundreds of thousands of pounds per year from 1988 through 2016. Underground injection dominated total reported releases, fluctuating between approximately 191,000 pounds (in 2003) and over 860,000 pounds (in 1992). On-site air emissions were in the range of tens of thousands of pounds annually. Since 1999, surface water discharges of nitrobenzene have not exceeded 500 pounds per year (USEPA, 2019a).

Nitrobenzene is expected to have a high likelihood of partitioning to water based on its water solubility. Multiple values for K_{oc} indicate that nitrobenzene is expected to have a moderate to high likelihood of partitioning to water, while the log K_{ow} and K_H indicate that nitrobenzene is expected to have a moderate likelihood of partitioning to water. Nitrobenzene is expected to have moderate persistence in water based on its aerobic biodegradation half-life (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

Nitrobenzene may have an adverse effect on the health of persons. NTP (1983) conducted a 90-day oral gavage study of nitrobenzene in F344 rats and B6C3F1 mice. The rats were more sensitive to the effects of nitrobenzene exposure than the mice, and changes in absolute and relative organ weights, hematologic parameters, splenic congestion, and histopathologic lesions in the spleen, testis, and brain were reported. Based on statistically significant changes in absolute and relative organ weights, splenic congestion, and increases in reticulocyte count and methemoglobin (metHb) concentration, a LOAEL of 9.38 mg/kg/day was identified for the subchronic oral effects of nitrobenzene in F344 male rats (USEPA, 2009f). This was the lowest dose studied, so a NOAEL was not identified. The mice were treated with higher doses and were generally more resistant to nitrobenzene toxicity, the toxic endpoints were similar in both species.

The testis, epididymis, and seminiferous tubules of the male reproductive system are targets of nitrobenzene toxicity in rodents. In male rats (F344/N and CD) and mice

toxicity database, extrapolation from subchronic to a chronic study duration, and LOAEL to NOAEL extrapolation.

[25] Approximately 99.9% of the metolachlor samples in NWIS are from ambient water. The highest finished water value in the NWIS data set is 0.24 µg/L, which is much lower than the HRL.

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(B6C3F1), nitrobenzene exposure via the oral and inhalation routes results in histopathologic lesions of the testis and seminiferous tubules, testicular atrophy, a large decrease in sperm count, and a reduction of sperm motility and/or viability, which contribute to a loss of fertility (NTP, 1983; Bond et al., 1981; Koida et al., 1995; Matsuura et al., 1995; Kawashima et al., 1995). These data suggest that nitrobenzene is a male-specific reproductive toxicant (USEPA, 2009f).

Under the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005b), nitrobenzene is classified as ''likely to be carcinogenic to humans'' by any route of exposure (USEPA, 2009f). A two-year inhalation cancer bioassay in rats and mice (Cattley et al., 1994; CIIT, 1993) reported an increase in several tumor types in both species. However, the lack of available data, including a physiologically based biokinetic or model that might predict the impact of the intestinal metabolism on serum levels of nitrobenzene and its metabolites following oral exposures, precluded the EPA's IRIS program from deriving an oral CSF (USEPA, 2009f). Additionally, a metabolite of nitrobenzene, aniline, is classified as a probable human carcinogen (B2) (USEPA, 1988).

Nitrobenzene has been shown to be non-genotoxic in most studies and was classified as, at most, weakly genotoxic in the 2009 USEPA IRIS assessment (ATSDR, 1990; USEPA, 2009f).

Of the available animal studies with oral exposure to nitrobenzene, the 90-day gavage study conducted by NTP (1983) is the most relevant study for deriving an RfD for nitrobenzene. This study used the longest exposure duration and multiple dose levels. Benchmark dose software (BMDS) (version 1.4.1c; USEPA, 2007c) was applied to estimate candidate PODs for deriving an RfD for nitrobenzene. Data for splenic congestion and increases in reticulocyte count and metHb concentration were modeled. The POD derived from the male rat increased metHb data with a benchmark response (BMR) of 1 standard deviation (SD) was selected as the basis of the RfD (see USEPA, 2009f for additional detail). Therefore, the benchmark dose level (BMDL) used as the POD is a $BMDL_{1SD}$ of 1.8 mg/kg/day.

In deriving the RfD, the EPA's IRIS program applied a composite UF of 1,000 to account for interspecies extrapolation (10), intraspecies variation (10), subchronic-to-chronic study extrapolation (3), and database deficiency (3) (USEPA, 2009f). Thus, the RfD calculated in the 2009 IRIS assessment is 0.002 mg/kg/day. The overall confidence in the RfD was medium because the critical effect is supported by the overall database and is thought to be protective of reproductive and immunological effects observed at higher doses; however, there are no chronic or multigenerational reproductive/developmental oral studies available for nitrobenzene. Because the critical effect in this study (increased metHb in the adult rat) is not specific to a sensitive subpopulation or lifestage, the general adult population was selected in deriving the HRL for regulatory determination.

The EPA calculated an HRL for the noncancer effects of nitrobenzene of 10 µg/L (rounded from 12.8 µg/L), based on the RfD of 0.002 mg/kg/day, using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 20% RSC factor.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that nitrobenzene does not occur with a frequency and at levels of public health concern in public water systems based on the EPA's evaluation of the following occurrence information.

The primary data for nitrobenzene are nationally-representative drinking water monitoring data generated through the EPA's UCMR 1 (USEPA, 2008b), collected from 2001 to 2003. UCMR 1 is the only dataset with nationally-representative finished water data for this contaminant. The EPA does not anticipate nitrobenzene occurrence meaningfully changing from the UCMR 1 monitoring period given that reported releases to surface water have generally decreased over time and detections of nitrobenzene in ambient waters and Six-Year Review monitoring data are at low levels. UCMR 1 collected 33,576 nitrobenzene samples from 3,861 PWSs. The contaminant was detected in only a small number of those samples (0.01%) above the HRL (10 µg/L), which is the same as the MRL (10 µg/L). The detections occurred in two large water systems (one surface water, the other groundwater); the maximum detected concentration of nitrobenzene was 100 µg/L.

Occurrence data for nitrobenzene in ambient water from the NAWQA program show that nitrobenzene was not detected in any of the samples collected under any of the three monitoring cycles. Non-NAWQA NWIS data show that nitrobenzene was detected in approximately 1% of samples (60 out of 7,265) and at approximately 1% of sites (25 out of 2,747). The median concentration among detections was 83.0 µg/L.

d. Statutory Criterion #3 (Meaningful Opportunity)

Nitrobenzene does not present a meaningful opportunity for health risk reduction for persons served by PWSs based on the estimated exposed population. UCMR 1 data indicate that the estimated population exposed to nitrobenzene above the HRL is 0.1%. As a result, the Agency finds that an NPDWR for nitrobenzene does not present a meaningful opportunity for health risk reduction.

e. Preliminary Regulatory Determination for Nitrobenzene

The Agency is making a determination to not regulate nitrobenzene with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that nitrobenzene may have an adverse effect on human health, the occurrence data indicate that nitrobenzene is not occurring or not likely to occur in PWSs with a frequency and at levels of public health concern, and regulation of such contaminant does not present a meaningful opportunity for health risk reduction for persons served by PWSs. Therefore, the Agency has determined that an NPDWR for nitrobenzene would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the First Unregulated Contaminant Monitoring Regulation (UCMR 1)* (USEPA, 2008b) present additional information and analyses supporting the Agency's evaluation of nitrobenzene.

7. RDX

a. Background

RDX is a nitrated triazine and is an explosive. The name RDX is an abbreviation of ''Royal Demolition eXplosive.'' The formal chemical name is hexahydro-1,3,5-trinitro-1,3,5-triazine (USEPA, 2019a). Annual production and importation of RDX in the United States was last reported by the EPA's CDR program in 2015 to be in the range of 1–10 million pounds. It appears to have held steady in that range from 2002 onward (USEPA, 2019a).

Studies have shown that this compound is mobile in soil and therefore likely to leach into groundwater (ATSDR, 2012a). RDX is expected to have a high likelihood of partitioning to water based on its log K_{ow} and K_H. Multiple values for K_{oc}

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indicate that RDX is expected to have a moderate to high likelihood of partitioning to water, while its water solubility indicates that RDX is expected to have a moderate likelihood of partitioning to water. RDX is expected to have low to moderate persistence based on modeled biodegradation rates (USEPA, 2019a).

b. Statutory Criterion #1 (Adverse Health Effects)

RDX may have adverse effects on the health of persons. Available health effects assessments include an IRIS toxicological review (USEPA, 2018e), and older assessments including an ATSDR toxicological profile (ATSDR, 2012a) and an OW assessment published in the 1992 *Drinking Water Health Advisory: Munitions* (USEPA, 1992). The EPA IRIS assessment (2018e) presents an RfD of 0.004 mg/kg/day based on convulsions as the critical effect observed in a subchronic study in F–344 rats by Crouse et al. (2006). The POD for the derivation was a $BMDL_{0.05}$ of 1.3 mg/kg/day derived using a pharmacokinetic model that identified the human equivalent dose (HED) based on arterial blood concentrations in the rats as the dose metric. A 300-fold UF (3 for extrapolation from animals to humans, 10 for interindividual differences in human susceptibility, and 10 for uncertainty in the database) was applied in determination of the RfD.

Additionally, the EPA IRIS assessment (USEPA, 2018e) classified data from the Lish et al. (1984) chronic study in $B6C3F_1$ as providing *suggestive evidence of carcinogenic potential* following the EPA (USEPA, 2005b) guidelines. The slope factor was derived from the lung and liver tumors' dose-response in the Lish et al. (1984) study. The POD for the slope factor was the $BMDL_{10}$ allometrically scaled to a HED yielding a slope factor of 0.08 per mg/kg/day.

In mice fed doses of 0 to 35 mg/kg/day for 24 months in the Lish et al. (1984) study, there were dose-dependent increases in adenomas or carcinomas of the lungs and liver in males and females (USEPA, 2018e). The formulation used contained 3 to 10% HMX, another munition ingredient. The EPA assessed the toxicity of HMX (USEPA, 1988). No chronic-duration studies were available to evaluate the carcinogenicity of HMX (USEPA, 1988). HMX is classified as Group D, or *not classifiable as to human carcinogenicity* (USEPA, 1992; USEPA, 1988). In the Levine et al. (1983) RDX dietary exposure study with Fischer 344 rats, a statistically significant increase in the incidence of hepatocellular carcinomas was observed in males but not in females (USEPA, 2018e). Although evidence of carcinogenicity included dose-dependent increases in two experimental animal species, two sexes, and two systems (liver and lungs), evidence supporting carcinogenicity in addition to the $B6C3F_1$ mouse study was not robust; this factor contributed to the *suggestive evidence of carcinogenic potential* classification. The EPA considered both the Lish et al. (1984) and Levine et al. (1983) studies to be suitable for dose-response analysis because they were well conducted, using similar study designs with large numbers of animals at multiple dose levels (USEPA, 2018e). The EPA (2018e) concluded that insufficient information was available to evaluate male reproductive toxicity from experimental animals exposed to RDX. In addition, the EPA (2018e) concluded that inadequate information was available to assess developmental effects from experimental animals exposed to RDX. The EPA selected the 2018 EPA IRIS assessment to derive two HRLs for RDX: The RfD-derived HRL (based on Crouse et al., 2006) and the oral cancer slope factor-derived HRL (based on Lish et al., 1984). The EPA has generally derived HRLs for ''possible'' or Group C carcinogens using the RfD approach in past Regulatory Determinations. However, for RDX, the EPA decided to show both an RfD-derived and oral-cancer-slope-factor-derived HRL since the mode of action for liver tumors is unknown and the 1×10^{-6} cancer risk level provides a more health protective HRL to evaluate the occurrence information.

The RfD-derived HRL for RDX was calculated using the RfD of 0.004 mg/kg/day based on a subchronic study in F–344 rats by Crouse et al. (2006) with convulsions as the critical effect (USEPA, 2018e). The point of departure for the RfD calculation was a human equivalent $BMDL_{0.05}$ of 1.3 mg/kg/day. The HED was derived using a pharmacokinetic model based on arterial blood concentrations in the rats as the dose metric. A 300-fold uncertainty factor (3 for extrapolation from animals to humans, 10 for interindividual differences in human susceptibility, and 10 for uncertainty in the database) was applied in determination of the RfD. The EPA calculated a RfD-derived HRL of 30 µg/L (rounded from 25.6 µg/L), for the noncancer effects of RDX based on the RfD of 0.004 mg/kg/day, using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 20% RSC factor.

The oral-cancer-slope-factor-derived HRL for RDX was also based on values presented in the 2018 EPA IRIS assessment. The slope factor is derived from the dose-response for lung and liver tumors in the Lish et al. (1984) study, with elimination of the data for the high dose group due to high mortality. The point of departure for the slope factor of 0.08 $(mg/kg/day)^{-1}$ was the $BMDL_{10}$ which was allometrically scaled to a HED. The EPA calculated an oral cancer slope factor-derived HRL of 0.4 µg/L for RDX based on the cancer slope factor of 0.08 $(mg/kg/day)^{-1}$, using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 1 in a million cancer risk level.

The EPA's (USEPA, 2018e) derivation of an oral slope factor for cancer is in accordance with the *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005b) while RDX is classified as having ''suggestive evidence of carcinogenic potential.'' Specifically, the guidelines state ''when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities'' (USEPA, 2005b). The EPA IRIS assessment concluded that the database for RDX contains well-conducted carcinogenicity studies (Lish et al., 1984; Levine et al., 1983) suitable for dose response and that the quantitative analysis may be useful for providing a sense of the magnitude and uncertainty of potential carcinogenic risk (USEPA, 2018e). Therefore, the EPA felt it was important to evaluate the occurrence information against both the RfD-derived HRL and the oral cancer slope factor-derived HRL.

c. Statutory Criterion #2 (Occurrence at Frequency and Levels of Public Health Concern)

The EPA proposes to find that RDX does not occur with a frequency and at levels of public health concern in public water systems based on the EPA's evaluation of the following occurrence information.

The primary data for RDX are nationally-representative drinking water monitoring data generated through the EPA's UCMR 2 a.m., collected from 2008 to 2010 (USEPA, 2015a). UCMR 2 is the only dataset with nationally-representative finished water data for this contaminant. Under UCMR 2, 32,150 RDX samples were collected from 4,139 PWSs. The contaminant was detected in only a small number of samples (0.01%) at or above the MRL (1 µg/L), which is about 2.5 times higher than the oral cancer slope factor-derived HRL (0.4 µg/L). The detections occurred

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in three large surface water systems; the maximum detected concentration of RDX was 1.1 µg/L and the median detected value was 1.07 µg/L.

Occurrence data for RDX in ambient water are not available from the NAWQA program; however, non-NAWQA data are available from NWIS. The NWIS data show that RDX was detected in approximately 46% of samples (517 out of 1,115 samples) and at approximately 29% of sites (43 out of 147 sites). The median concentration based on detections was 26.0 µg/L (the 99th percentile was 120 µg/L and the maximum value was 310 µg/L). While the NWIS data show that ambient waters contain detectable levels of RDX, the nationally-representative drinking water monitoring data indicate that only a small number of samples are at or above the MRL; Section III.a.3 notes that ambient water data are a less important factor in making a regulatory determination.

d. Statutory Criterion #3 (Meaningful Opportunity)

RDX does not present a meaningful opportunity for health risk reduction for persons served by PWSs based on the estimated exposed population, including sensitive populations. UCMR 2 findings indicate that the estimated population exposed to RDX at or above the MRL is 0.04%. As a result, the Agency finds that an NPDWR for RDX does not present a meaningful opportunity for health risk reduction. Based on the small number of samples measured at or marginally above the MRL, the EPA does not believe that there would be enough occurrence in the narrow range between the HRL and the MRL to change our meaningful opportunity determination.

e. Preliminary Regulatory Determination for RDX

The Agency is making a preliminary determination to not regulate RDX with an NPDWR after evaluating health, occurrence, and other related information against the three SDWA statutory criteria. While data suggest that RDX may have an adverse effect on human health, the occurrence data indicate that RDX is not occurring or not likely to occur in PWSs with a frequency and at levels of public health concern. Therefore, the Agency has determined that an NPDWR for RDX would not present a meaningful opportunity to reduce health risk for persons served by PWSs. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Second Unregulated Contaminant Monitoring Regulation (UCMR 2)* (USEPA, 2015a) present additional information and analyses supporting the Agency's evaluation of RDX.

V. Status of the Agency's Evaluation of Strontium, 1,4-Dioxane, and 1,2,3-Trichloropropane

A. Strontium

Strontium is an alkaline earth metal. On October 20, 2014 the Agency published its preliminary regulatory determination to regulate strontium and requested public comment on the determination and supporting technical information (USEPA, 2014a). Informed by the public comments received, rather than making a final determination for strontium in 2016, the EPA delayed the final determination to consider additional data, and to decide whether there is a meaningful opportunity for health risk reduction by regulating strontium in drinking water (USEPA, 2016a). Specifically, the notification on the delayed final determination mentioned that the EPA would evaluate additional studies on strontium exposure and health studies related to strontium exposure. Since 2016, the EPA has worked to identify and evaluate published studies on health effects associated with strontium exposure, sources of exposure to strontium, and treatment technologies to remove strontium from drinking water. In this document, the EPA is clarifying that it is continuing with its previous 2016 decision (USEPA, 2016a) to delay a final determination for strontium in order to further consider additional studies related to strontium exposure.

With the preliminary regulatory determination in 2014, the EPA published a peer-reviewed HESD for strontium (USEPA, 2014c) and an HRL of 1,500 µg/L. That document addresses exposure from drinking water and other media, toxicokinetics, hazard identification, and dose-response assessment, and provides an overall characterization of the risk from drinking water containing strontium.

The chemical similarity of strontium to calcium allows it to exchange for calcium in a variety of biological processes, which could result in detrimental health effects. The most important of these processes is the substitution of calcium in bone, affecting skeletal development. Because the mode of action for this adverse effect is strontium uptake into bone, the toxicity of strontium depends on an individual's stage of bone development and their intake of nutrients related to bone formation, such as calcium, magnesium, phosphorous and Vitamin D. Infants, children and adolescents with low dietary intakes of bone forming nutrients are among the most vulnerable to exposures to high levels of strontium during periods of bone growth (USEPA, 2014c). Women who are pregnant or lactating may also be sensitive to strontium due to their increased requirement for bone-forming nutrients and increased rates of bone remodeling. Breast-fed infants (from exposure to lactating mothers who have an increased water intake), formula-fed infants (who will ingest a greater volume of contaminated water), and the developing fetus (from exposure to pregnant women who have an increased water intake) are other susceptible subpopulations. In these populations and lifestages, susceptibility is enhanced by a combination of high exposure and lifestage.

Toxicity studies indicate that strontium can decrease the calcification of the cartilaginous portion of bone. The results of animal studies show that the effects of strontium at doses from 400–500 mg Sr/kg/day include small changes in bone structure and inhibition of calcification, consistent with early development of osteomalacia and/or ''strontium rickets.'' Decreased levels of osteoclasts and associated decreases in bone resorption can also occur at these doses in animals. Higher doses of strontium can result in more severe bone effects including reduced growth, large areas of unmineralized bone, bone softening (''strontium rickets'' in young animals, and osteomalacia in adults), excess growth of epiphyseal cartilage, and abnormal deposition of osteoid in the metaphyses (USEPA, 2014c). More recent information on strontium toxicity is now available in the peer reviewed literature. The EPA intends to do an updated literature search and systematic review before finalizing the assessment.

The primary finished drinking water occurrence data for strontium are recent (2013–2015) nationally-representative drinking water monitoring data generated through the EPA's UCMR 3. Under the UCMR 3, 62,913 samples were analyzed for strontium; 2.8% of those samples were found at concentrations greater than the HRL (potentially subject to change following examination of health studies), and 99.8% of the samples were found at concentrations greater than the MRL (0.3 µg/L). In addition, approximately 5.8% of the PWSs had at least one detection greater than the HRL, corresponding to 6.2% of the U.S. population.

The EPA evaluated several treatment-related studies concerning strontium's removal from drinking water. A full-

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scale evaluation of strontium removal from groundwater sources at four lime softening and four ion exchange softening plants in Ohio was reported by Lytle et al. (2017). Raw waters contained between 13 and 28 mg/L, and 1.2 and 15 mg/L strontium at the ion exchange and lime softening plants, respectively. Ion exchange effectively removed nearly all of the strontium, although under typical operation, treated strontium levels were dictated by the percentage of water that by-passed the ion exchange vessels. The amount of strontium that was removed by lime softening ranged between 49 and 94% on average (or to final levels of between 0.2 and 3.6 mg/L) likely dependent on treatment and water quality conditions.

O'Donnell et al. (2016) evaluated the effectiveness of conventional treatment (*i.e.,* coagulation/filtration) and lime-soda ash softening treatment methods to remove strontium from drinking water. The results indicated that coagulation/filtration was ineffective at removing strontium (6–12% removal) and lime-soda ash softening was more effective, with removal percentages as high as 78%. Additionally, the authors noted that the removal of strontium using lime-soda ash softening in all of the softening jar tests was directly associated with substantial calcium removal, typically at higher rates compared to the removal of strontium.

Najm (2016) reviewed available literature for the removal of naturally occurring stable strontium or anthropogenically produced radioactive strontium from drinking water. The main conclusion was that precipitative softening (*i.e.,* lime-soda ash softening) and cation-exchange are the most feasible options. Additionally, the report highlights that chemical precipitation is targeted for the removal of calcium or magnesium and it is unknown if targeted removal of strontium can be achieved. Likewise, partial removal of calcium is unavoidable with cation exchange, even in a process targeted for strontium removal.

While the EPA determined in 2014 that strontium may have adverse effects on the health of persons including children, the Agency continues to consider additional data, consult existing assessments (such as ATSDR's Toxicological Profile from 2004 and Health Canada's Drinking Water Guideline from 2018), and evaluate whether there is a meaningful opportunity for health risk reduction by regulating strontium in drinking water. Additionally, the EPA understands that strontium may co-occur with beneficial calcium in some drinking water systems and treatment technologies that remove strontium may also remove calcium. The agency is evaluating the effectiveness of treatment technologies under different water conditions, including calcium concentrations.

B. 1,4-Dioxane

The EPA is not making a preliminary determination for 1,4-dioxane at this time as the Agency has not determined whether there is a meaningful opportunity for public health risk reduction. As discussed in Section II.B.1 of this document, the EPA considers three statutory criteria mandated under SDWA Section 1412(b)(1)(A) in making a decision to regulate a contaminant. The EPA summarizes the current status of its evaluation of 1,4-dioxane below. The EPA will continue to evaluate 1,4-dioxane in the context of all three statutory criteria prior to making such a proposal as part of a future regulatory determination.

1,4-Dioxane is used as a solvent in cellulose formulations, resins, oils, waxes, and other organic substances; also used in wood pulping, textile processing, degreasing; in lacquers, paints, varnishes, and stains; and in paint and varnish removers.

Health effects information for 1,4-dioxane are available from several sources including EPA IRIS (USEPA, 2010b), ATSDR (2012b), and WHO (2005). The EPA's IRIS assessment (USEPA, 2010b) shows critical effects for both noncancer (liver, kidney, and nasal toxicity) and cancer (hepatocellular adenoma and carcinoma) endpoints.

The EPA's IRIS identified an oral reference dose (RfD) for 1,4-dioxane of 0.03 mg/kg/day based on the Kociba (1974) 2-year rat feeding study in which hepatic and renal toxicity in male rats were identified as critical effects (Kociba, 1974; USEPA, 2010b; USEPA, 2013). The LOAEL of 94 mg/kg/day was based on hepatocellular degeneration and necrosis as well as renal tubule epithelial cell degenerative changes and necrosis in male Sherman rats, with a NOAEL of 9.6 mg/kg/day. A composite UF of 300 was applied to the RfD to account for pharmacokinetic and pharmacodynamic differences between rats and humans (10); interindividual variability (10); and database deficiencies (3) (USEPA, 2010b; USEPA, 2013).

In 2013, the EPA IRIS classified 1,4-dioxane as ''likely to be carcinogenic to humans'' in accordance with the EPA's 2005 *Guidelines for Carcinogenic Risk Assessment,* based on evidence of carcinogenicity in two-year studies performed with three strains of rats, two strains of mice, and guinea pigs. The MOA by which 1,4-dioxane induces tumors in animal models is not conclusive, so a linear low dose extrapolation was used to estimate human carcinogenic risk (USEPA, 2013).

For the HRL derivation, the EPA selected the oral cancer slope factor of 0.10 $(mg/kg/day)^{-1}$ for 1,4-dioxane derived by the EPA IRIS for hepatocellular adenomas or carcinomas in female mice (2013). The principal study selected for the derivation of an oral cancer slope factor was Kano et al., 2009.[26] The oral cancer slope factor was derived using linear extrapolation from the point of departure (POD) (*i.e.,* the 95% lower confidence limit on the dose associated with a benchmark response near the lower end of the observed data) calculated by fitting a curve to the experimental dose-response data using log-logistic benchmark dose modeling. The EPA (USEPA, 2013) indicated that a multistage model did not provide an adequate fit because of the steep rise in the dose-response curve from the low-dose to the mid-dose followed by a plateau between the mid- and high-dose groups for the hepatocellular adenoma or carcinoma incidence data in the female mice (USEPA, 2013). The EPA performed a comparison of benchmark dose (BMD) and benchmark dose limit (BMDL) estimates derived for studies of rats and mice and found that female mice are more sensitive to 1,4-dioxane induced liver carcinogenicity than other species or types of tumors (USEPA, 2013). The EPA therefore derived an oral cancer slope factor of 0.10 $(mg/kg/day)^{-1}$ for 1,4-dioxane using the BMDL HED for hepatocellular adenomas or carcinomas in female mice with a benchmark response of 50% as the POD (USEPA, 2013). The EPA calculated an HRL for 1,4-dioxane of 0.32 µg/L based on the cancer slope factor of 0.1 $(mg/kg/day)^{-1}$, using 2.5 L/day drinking water ingestion, 80 kg body weight, and a 1 in a million cancer risk level. The EPA recently released a draft risk evaluation for 1,4-dioxane (USEPA, 2019f) that includes an oral slope factor different than that provided by IRIS (USEPA, 2010b). Additionally, Health Canada released a guideline technical document for 1,4-dioxane for public consultation in 2018 (Health Canada, 2018). The consultation period ended November 9, 2018 and a final publication is pending.

[26] Note that the study results for the two-year drinking water study have been reported in multiple publications and/or communications (Kano et al., 2009; Yamazaki et al., 1994; JBRC, 1998; and Yamazaki, 2006).

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Once completed, the EPA will consider whether either the newer EPA oral slope factor or Canadian guideline technical document is appropriate to inform a regulatory determination.

The primary occurrence data for 1,4-dioxane are recent (2013–2015) nationally-representative drinking water monitoring data generated through the EPA's UCMR 3. Under the UCMR 3, 36,810 samples were analyzed for 1,4-dioxane; 3.4% of those samples were found at concentrations greater than the HRL, and 11.4% of the samples were found at concentrations greater than the MRL (0.07 µg/L). In addition, approximately 7.8% of the PWSs had at least one detection greater than the HRL.

While the health effects data suggest that 1,4-dioxane may have an adverse effect on human health and the occurrence data indicate that 1,4-dioxane is occurring in finished drinking water above the HRL, the EPA continues to evaluate whether there is a meaningful opportunity to reduce health risk for persons served by PWSs by establishing an NPDWR for 1,4-dioxane. Based on UCMR 3 data, the EPA derived a national estimate of less than two baseline cancer cases per year attributable to 1,4-dioxane in drinking water. The EPA derived this estimate by using the CSF from the IRIS assessment (USEPA, 2013), a national extrapolation of UCMR 3 population-weighted mean exposure data, and the assumption that all UCMR 3 non-detect samples were equivalent to the MRL (0.07 µg/L), which was intended to result in a high-end estimate of the number of national cancer cases. However, while the number of baseline cancer cases is relatively low, other adverse health effects following exposure to 1,4-dioxane may also contribute to potential risk to public health, and these analyses have not yet been completed.

As the EPA evaluates whether there is a meaningful opportunity to protect public health by establishing a national-level drinking water regulation for 1,4-dioxane, the Agency recognizes that several states have ongoing activities relevant to control of 1,4-dioxane in PWSs. For example, New York State has a recommended MCL of 1.0 µg/L,[27] and California has a notification level of 1 µg/L.[28] Based on UCMR 3 data, 38% of systems where system averages of 1,4-dioxane were greater than the HRL are in California and New York.

The Agency is not making a preliminary determination for 1,4-dioxane at this time as the Agency has not determined whether there is a meaningful opportunity for public health risk reduction. The Agency intends to complete its new risk evaluation for 1,4-dioxane that is currently in draft (USEPA, 2019f) and consider it and the Canadian guideline technical document and other relevant new science prior to making a regulatory determination. This evaluation may provide clarity as to whether there is a meaningful opportunity for an NPDWR to reduce public health risk. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of 1,4-dioxane.

C. 1,2,3-Trichloropropane

1,2,3-Trichloropropane is a man-made chemical used as an industrial solvent, cleaning and degreasing agent, and synthesis intermediate. Due to analytical method-based limitations, the EPA is not making a preliminary determination on 1,2,3-trichloropropane at this time.

Health effects information for 1,2,3-trichloropropane is available from EPA IRIS (USEPA, 2009g), EPA OW (USEPA, 1989b), ATSDR (1992b; 2011), and California OEHHA (2009). The most recent health assessment is the EPA's IRIS assessment (USEPA, 2009g), which uses an NTP study (NTP, 1993) to derive both an RfD of 0.004 mg/kg/day for noncancer effects and a CSF of 30 (mg/kg/day)$^{-1}$. The NTP (1993) chronic duration oral bioassay gavage study of rats and mice shows critical effects for both noncancer (increased liver weight) and cancer endpoints (alimentary system squamous cell neoplasms, liver hepatocellular adenomas or carcinomas, Harderian gland adenoma, uterine/cervix adenomas or carcinomas) for oral exposure. 1,2,3-Trichloropropane received a classification of ''likely to be carcinogenic to humans'' based on statistically significant increases in multiple tumors types in rats and mice.

The HRL for the cancer effects is based on the EPA IRIS cancer slope factor for 1,2,3-trichloropropane of 30 (mg/kg/day)$^{-1}$ (USEPA, 2009g). The oral cancer slope factor was calculated for adult exposures and does not take into account presumed early-life susceptibility to 1,2,3-trichloropropane exposure. As outlined in the IRIS assessment, the evidence indicates that 1,2,3-trichloropropane carcinogenicity occurs via a mutagenic MOA. The EPA provides guidance on assessing early life carcinogen exposure (USEPA, 2005b; USEPA, 2005c), and children potentially exposed to mutagenic carcinogens can be assumed to have the potential for increased early-life susceptibility to carcinogens. Therefore, for mutagenic carcinogens, the EPA recommends that risk assessors apply special adjustment factors to a given cancer slope factor which are dependent on age (ADAFs). Section 5.4.5 of the IRIS assessment for 1,2,3-trichloropropane describes application of the ADAFs to the CSF. The EPA recommends the application of these ADAFs when estimating cancer risks from early life (<16 years of age) exposure to 1,2,3-trichloropropane (USEPA, 2009g). Thus, the EPA calculated an HRL of 0.0004 µg/L (0.4 ng/L) using ADAFs and a cancer risk level of one cancer case per million people.

The primary occurrence data for 1,2,3-trichloropropane are nationally-representative drinking water monitoring data generated through the EPA's UCMR 3 (2013–2015). Under the UCMR 3, an MRL of 0.03 µg/L was identified for the method used to analyze that contaminant (EPA Method 524.3).[29] For the 36,848 samples collected during UCMR 3, 0.69% of the samples exceeded the MRL. Further, about 1.4% of PWSs had at least one detection over the MRL, corresponding to 2.5% of the population.

While the UCMR 3 data indicated 1,2,3-trichloropropane occurrence was relatively low at concentrations above the MRL, the MRL (0.03 µg/L) is more than 75 times the HRL (0.0004 µg/L) for 1,2,3-trichloropropane. This discrepancy allows for a broad range of potential contaminant concentrations that could be in exceedance of the HRL but below the MRL. Thus, the EPA needs additional lower-level occurrence information prior to making a preliminary regulatory determination

[27] In December 2018, the New York State Departments of Health and Environmental Conservation announced that the New York State Drinking Water Quality Council has recommended that the Department of Health ''adopt an MCL for 1,4-dioxane of 1.0 part per billion'' (*i.e.,* 1.0 µg/L). New York State approved Advanced Oxidative Process (AOP) as an effective treatment technology for 1,4-dioxane.

[28] The California drinking water notification level for 1,4-dioxane is 1 µg/L. The response level, the level at which the source is removed from service, is 35 µg/L. The notification level is slightly greater than the de minimis (1 X 10E–6) level commonly used for notification levels based on cancer risk, reflecting difficulty in monitoring 1,4-dioxane at very low concentrations.

[29] Under UCMR 3, the MRL for an analyte, as determined by a specified analytical method, is a reporting threshold set at a level at which quantitation is achievable, with 95% confidence, by a capable analyst/laboratory at least 75% of the time when using the specified analytical method. This simultaneously accounts for both precision and accuracy.

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for 1,2,3-trichloropropane. The *Regulatory Determination 4 Support Document* (USEPA, 2019a) and the *Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3)* (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of 1,2,3-trichloropropane.

VI. EPA's Request for Comments and Next Steps

The EPA invites commenters to submit any relevant data or information pertaining to the preliminary regulatory determinations identified in this document, as well as other relevant comments. The EPA will consider the public comments and/or any new, relevant data submitted for the contaminants discussed in this document and in the supporting rationale.

The data and information requested by the EPA include peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices, and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the review justifies use of the data).

Peer-reviewed data are studies/analyses that have been reviewed by qualified individuals (or organizations) who are independent of those who performed the work, but who are collectively equivalent in technical expertise (*i.e.,* peers) to those who performed the original work. A peer review is an in-depth assessment of the assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria, and conclusions pertaining to the specific major scientific and/or technical work products and the documentation that supports them (USEPA, 2015b).

Specifically, the EPA is requesting comment and/or information related to the following aspects:

- The health effects information considered by the Agency in making the preliminary determinations described in this document. The EPA requests commenters identify any additional peer reviewed studies that could inform the final regulatory determination.
- Drinking water occurrence information considered by the Agency in making the preliminary determinations described in this document. The EPA requests commenters identify any additional data and studies upon the occurrence of these contaminants in drinking water.
- The EPA requests comment on what additional information the Agency should consider in developing a NPDWR for PFOA and PFOS beyond the information described in this document. The EPA notes that ongoing evaluations of PFOA and PFOS health effects include the National Toxicology Program's Technical Report on the Toxicology and Carcinogenesis Studies of PFOA, ATSDR toxicity assessments, as well as state health assessments.
- The EPA requests comment upon potential regulatory constructs, grouping approaches, and potential monitoring requirements described in Sections III.A.1. and IV.B.1.f of this document.
- The EPA requests additional studies and data that characterizes the occurrence of PFAS in drinking water. The Agency is particularly interested in datasets that include:
  - Information on the sample data that includes: Location and sample type (raw or treated water; groundwater or surface water source);
  - Information on the measurement results that includes: Specific analyte, analytical method used; measurement results; units and qualifiers; detection limit values (for non-detects);
  - Sample collection dates for a given sample and analysis dates for each analytical result;
  - Meta data that could include the organization that created the dataset; contact information; the purpose of the data collection; the size of the dataset; and indication of data quality (such as a quality assurance project plan); and
  - An accompanying data dictionary and reference to Quality Assurance processes for sample collection and analysis information.
- The EPA requests peer reviewed health effects studies for PFAS other than PFOA and PFOS that the Agency could consider in future regulatory decision making.
- Specific information about removal of PFOA, PFOS, and other PFAS from drinking water under field conditions, including information about effectiveness and costs of various treatment approaches and effectiveness of PFAS removal in the presence of other contaminants and constituents.

The EPA intends to carefully evaluate the public comments received on the eight preliminary determinations and issue its final regulatory determinations. If the Agency makes a final determination to regulate any of the contaminants, the EPA intends to propose an NPDWR within 24 months and promulgate a final NPDWR within 18 months following the proposal.[30] In addition, the EPA will also consider information provided about the three contaminants discussed in Section V to inform potential future regulatory determinations.

[30] The statute authorizes a nine-month extension of this promulgation date.

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