PROTOCOL FOR THE DERIVATION OF ENVIRONMENTAL QUALITY GUIDELINES FOR THE PROTECTION OF APEX MARINE MAMMALS FROM BIOACCUMULATIVE SUBSTANCES

NOTE TO READER

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Sections 5, 6 and 7 of this document in their entirety are reproduced from "A framework for the derivation of environmental quality guidelines that protect apex marine mammals from persistent organic pollutants (POPs)" (McTavish *et al.* 2024) with minor changes.

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GLOSSARY

Apex marine mammal: Marine mammal species and species functional group at the top of the food chain (food web) with no natural predators in its environment.

Bioaccumulation: Process by which aquatic organisms accumulate chemical substances directly from water or through the consumption of food containing the chemicals (Canadian Council of Resource and Environment Ministers [CCREM] 1987).

Bioconcentration: Process by which there is a net accumulation of a chemical directly from water within aquatic organisms resulting from simultaneous uptake (e.g., by gill or epithelial tissue) and elimination (CCREM 1987).

Biomagnification: Result of the processes of bioconcentration and bioaccumulation by which tissue concentrations of bioaccumulated chemicals increase as the chemical passes up through two or more trophic levels. The term implies an efficient transfer of chemicals from food to consumer so that residue concentrations increase systematically from one trophic level to the next (CCREM 1987).

Biomarker: Physiological, histological or biochemical measurement indicating that an organism has experienced stress from contaminant exposure.

Biomonitoring: Monitoring biological components of ecosystems (e.g., biomarkers, species presence or absence, diversity) to estimate organismic or ecosystem stress.

Environmental Quality Guideline (EQG): Scientifically derived numerical concentration or narrative statement describing what is considered to be protective of designated values in ambient conditions.

K_{OC}: Organic carbon-water partition coefficient. It is a parameter that is used to express the extent to which an organic chemical partitions itself between the soil or sediment and solution phases.

K_{OW}: Octanol/water partition coefficient. The ratio of a chemical's solubility in n-octanol and water at equilibrium. The logarithm of K_{OW} is used as an indication of a chemical's propensity for bioconcentration by aquatic organisms (CCREM 1987).

Mode of action (MOA): Cellular or molecular mechanisms through which a toxic substance exerts its harmful effects on an organism.

Point of departure (POD): Point in a toxicological dose-response data set generally corresponding to an estimated low effect level or no effect level (e.g., benchmark dose lower confidence limit [BMDL], effect concentration affecting 10% of the test organisms [EC10], no observed adverse effect level [NOAEL], lowest observed adverse effect level [LOAEL]).

Tissue residue: Chemical substance in aquatic biota tissue, such as fish, shellfish, invertebrates and aquatic plants, on a whole-body, wet-weight basis.

Toxicity reference value (TRV): Parameter used to quantitatively assess potential risks to human health or the environment that are associated with exposure to a chemical or contaminant of concern.

Trophic magnification factor (TMF): Diet-weighted average biomagnification factor (BMF) of chemical residues across food webs.

Weight of evidence (WoE): Method for decision-making that involves the consideration of multiple sources of information and lines of evidence.

LIST OF ACRONYMS

ADME	absorption, distribution, metabolism and excretion
AOP	adverse outcome pathway
ATSDR	Agency for Toxic Substances and Disease Registry
BAF	bioaccumulation factor
BC ENV	British Columbia Ministry of Environment and Climate Change Strategy
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMF	biomagnification factor
BSAF	biota-sediment accumulation factor
bw	body weight
CCME	Canadian Council of Ministers of the Environment
CCREM	Canadian Council of Resource and Environment Ministers
CDG_{mm}	Canadian dietary guideline for the tissue of marine mammal prey
CEQG	Canadian Environmental Quality Guideline
$CEQG_{mm}$	Canadian Environmental Quality Guideline for the protection of marine mammals
$CSeQG_{mm}$	Canadian Sediment Quality Guideline for the protection of marine mammals
$CWQG_{mm}$	Canadian Water Quality Guideline for the protection of marine mammals
DFO	Fisheries and Oceans Canada
DG_{mm}	dietary guideline for the protection of marine mammals
ECCC	Environment and Climate Change Canada
ECx	effect concentration causing response in x% of test organisms
EQG_{mm}	environmental quality guideline for the protection of marine mammals
FI:BW	rate of food intake to body weight
IBM	individual-based model
KC	key characteristic
K_{OC}	organic carbon-water partition coefficient
K_{OW}	octanol-water partition coefficient
LOAEL	lowest observable adverse effect level
MATC	maximum acceptable toxicant concentration
MDL	method detection limit
MoA	mode of action

186	MoD	method of detection
187	NOAEL	no observable adverse effect level
188	OC	organic carbon
189	PAH	polycyclic aromatic hydrocarbon
190	PBDE	polybrominated diphenyl ether
191	PBT	persistent, bioaccumulative and toxic
192	PCB	polychlorinated biphenyl
193	PFAS	per- and polyfluoroalkyl substances
194	POD	point of departure
195	POP	persistent organic pollutant
196	QSAR	quantitative structure-activity relationship
197	$SeQG_{mm}$	sediment quality guideline for the protection of marine mammals
198	SLEB	St. Lawrence Estuary beluga
199	SRKW	Southern resident killer whale
200	TMF	trophic magnification factor
201	TOC	total organic carbon
202	TRV	toxicity reference value
203	UF	uncertainty factor
204	US EPA	United States Environmental Protection Agency
205	WoE	weight of evidence
206	WQG_{mm}	water quality guideline for the protection of marine mammals

1. INTRODUCTION

This document outlines the procedures for deriving consistent and scientifically defensible Canadian Environmental Quality Guidelines (CEQGs) for the protection of apex marine mammals against organic contaminants deemed to be persistent, bioaccumulative and toxic (PBTs). An apex predator is a species at the top of the food chain with no natural predators in their environment. PBT contaminants are those that are resistant to degradation from biotic or abiotic factors, accumulate in biota over time and increase with each trophic level in aquatic food webs. In some marine mammals, concentrations of these contaminants can reach levels that can elicit harm to endocrine, immune and reproductive systems (Desforges *et al.* 2016; Fair and Houde 2023; Mos *et al.* 2010; Ross *et al.* 1996). Contaminants are considered a primary anthropogenic threat to several marine mammal species and populations, including the endangered St. Lawrence Estuary beluga (SLEB, *Delphinapterus leucas*), the Southern resident killer whale (SRKW, *Orcinus orca*), also called the orca whale, and many other species listed under the *Species at Risk Act* (SARA) (Committee on the Status of Endangered Wildlife in Canada [COSEWIC] 2018; Department of Fisheries and Oceans [DFO] 2018).

Apex marine mammals are typically long-lived and are not able to metabolize, bio-transform or excrete persistent contaminants to reduce their body burden. This results in the accumulation of contaminants over many years and over many generations, increasing the risk of elevated chemical burdens (Alava and Gobas 2012). Apex marine mammals have high lipid tissue content (e.g., blubber) in their bodies and rely on fat storage for energy in various situations (e.g., during times of low prey availability or nutritional stress; Banfield 1974). Most organic contaminants are lipid-soluble and therefore stored in the blubber (Mos *et al.* 2010; Ross *et al.* 1996). Females transfer significant quantities of persistent contaminants to their offspring *in utero* via the placenta or through lactation (i.e., maternal transfer) (Barrett *et al*. 2021; Desforges *et al*. 2012; Lee *et al*. 2023). In addition to chemical contamination, marine mammals are often sensitive and vulnerable to other anthropogenic stressors that act cumulatively, including prey availability, vessel and physical disturbance and climate change (Alava *et al*. 2018).

In this document, a protocol is presented for the derivation of Canadian Environmental Quality Guidelines for the Protection of Apex Marine Mammals ($CEQGs_{mm}$) from bioaccumulative substances, herein referred to as "this protocol." The approach outlined in this protocol was produced by the Marine Mammal Protocol Sub-Committee of the Southern Resident Killer Whale Contaminants Technical Working Group and published previously (McTavish *et al.* 2024). This approach is based on methodologies used in the Canadian Council of Ministers of the Environment (CCME) protocol for deriving wildlife tissue residue guidelines (CCME 1998) as well as human health risk assessment methodologies. In this protocol, available marine mammal data are combined with rodent data generated for human health assessments to support a weight-of-evidence (WoE) approach to guideline development. Ecological modelling is then used to calculate $CEQGs_{mm}$ from PBT substances for three environmental compartments: marine mammal prey tissue, sediment and water. The general steps of guideline derivation are summarized in Figure 1 and are further explained through the rest of this document.

This document provides a method to derive $CEQGs_{mm}$ from PBT substances by including more sensitive endpoints applicable to the protection of vulnerable individuals, instructions for use of

toxicity reference values (TRVs) derived for humans, biomagnification factors (BMFs) to account for contaminant accumulation in apex marine mammals, and a modelling approach to calculate guideline values in sediment and water as well as prey tissue.

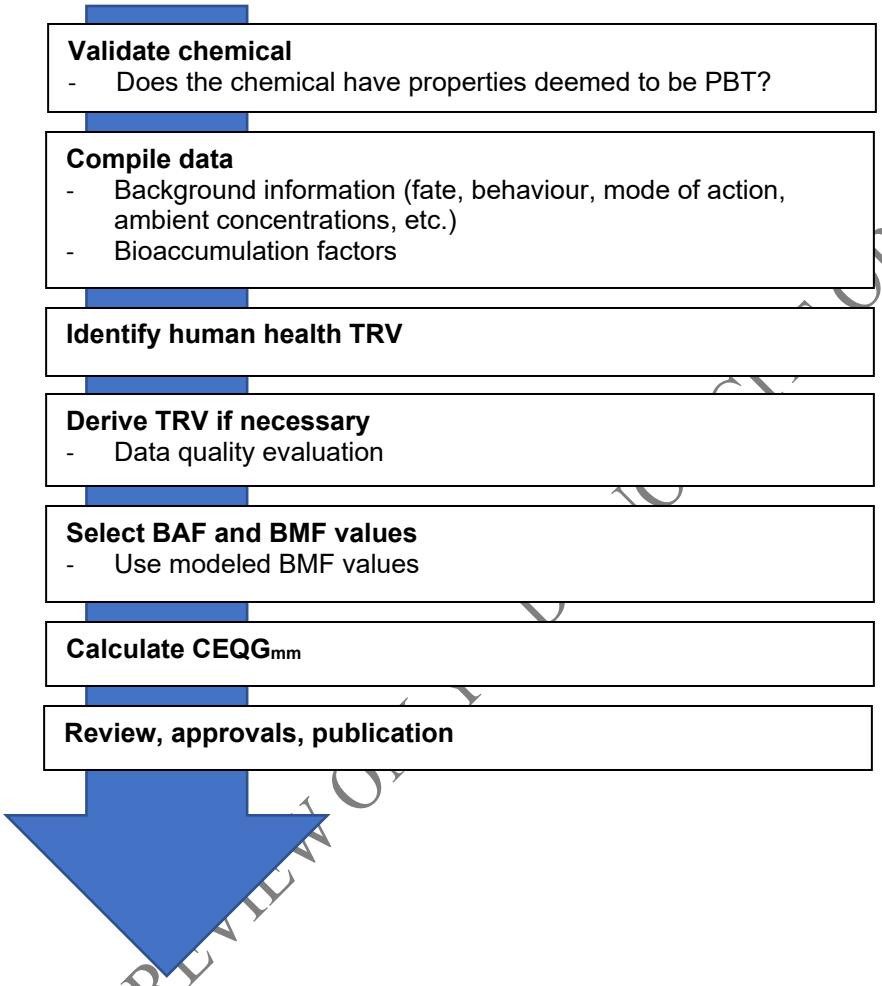

Figure 1. General Steps for the Derivation of Canadian Environmental Quality Guidelines for the Protection of Apex Marine Mammals from Organic Contaminants That Are Persistent, Bioaccumulative and Toxic

Notes:
BAF = bioaccumulation factor; BMF = biomagnification factor; $CEQG_{mm}$ = Canadian Environmental Quality Guideline for the protection of marine mammals; PBT = persistent, bioaccumulative and toxic; TRV = toxicity reference value.

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1.1 Background

CEQGs are developed by CCME using formal protocols to provide a consistent, scientifically defensible approach for assessing and managing toxic substances in the environment. These guidelines provide numerical concentrations or narrative statements describing the maximum recommended concentrations that should be present in various media (i.e., water, sediment, tissue and soil) to protect, enhance and restore designated environmental values and species. CEQGs provide benchmarks to help interpret biological monitoring data and serve as the scientific basis

for determining interim management objectives and performance indicators to measure progress in virtual elimination strategies. They do not have any direct legal standing unless prescribed by regulation or binding agreements. An exceedance of a CEQG does not necessarily imply that unacceptable risks are present, but that the potential for adverse effects is increased and additional investigation and monitoring are warranted.

1.2 Guiding Principles

- Guidelines are generic (i.e., not species- or site-specific) Canada-wide recommendations that are based on the most current scientific information available at the time of their derivation. They do not directly consider site-specific, technological, socioeconomic or management factors that may influence their implementation.
- Guidelines are meant to protect all apex marine mammals in Canada and all aspects of their life stages or cycles, including the most sensitive life stage of the most sensitive species indefinitely (i.e., chronic exposures or shorter-term exposure during periods of development), from the negative effects of exposure to toxic substances. Therefore, guideline derivation should focus on the most sensitive sub-population, which is often neonates or nursing juveniles.
- $CEQGs_{mm}$ are intended to protect individuals of the population, which in turn also protects populations and communities. This is a necessary consideration for marine mammals that are top predators and, in some cases, endangered (e.g., SRKW). This approach may not protect individuals already weakened through age, illness, injury or cumulative stress from climate change, declining prey availability and shipping-related disturbance.
- Guideline derivation assumes the main route of exposure to PBT substances for apex marine mammals is the consumption of contaminated aquatic prey. Other routes of exposure may be incorporated if deemed necessary.
- Guideline derivation should follow a WoE approach (see Section 5.4) that considers data from all valid sources, including marine mammal biomarker data and laboratory animal data, to support decisions.
- Guideline derivation must be done in a clear and transparent manner and, whenever possible, follow the process outlined in this document.

2. SELECTION OF SUBSTANCES FOR GUIDELINE DEVELOPMENT

This protocol is specifically intended for organic substances that are persistent, bioaccumulative and toxic. PBT chemicals typically have a bioconcentration factor (BCF) or bioaccumulation factor (BAF) of ≥5,000 or a log octanol-water partition coefficient (K_{OW}) of ≥5 and are persistent in the environment (e.g., half-lives in water and sediment of ≥182 days and ≥365 days, respectively) (Gobas *et al.* 2009; Government of Canada 2000). The definitions of "persistent" and "bioaccumulative" adopted here align with those of the *Canadian Environmental Protection Act* (Government of Canada 2000).

For derivation of CEQGs to proceed, there must be evidence that marine mammals are being exposed to the substance or substance group. This will be confirmed via published, peer-reviewed

studies or government monitoring data that documents the substance's presence in marine mammal tissue or its prey. In accordance with the precautionary principle, monitoring data that indicate the environmental presence of the substance, its associated negative effects, and the likelihood of continued or future exposure should all be considered when determining if guideline development is necessary. This protocol may be used by multiple jurisdictions in Canada which may have additional criteria for selecting priorities. Therefore, the selection of substances for guideline development may vary across jurisdictions.

Given the complexity associated with developing $CEQGs_{mm}$, including those associated with ecological modelling, this protocol is offered as a framework for guideline derivation. Elements of this framework may not provide the best methodology for some substances. In these cases, the guiding principles of this protocol must be followed, and an effort made to include as many of the protocol's elements as possible in guideline derivation. Further, the process must be documented in a clear and transparent manner.

2.1 Mixture Considerations

Many organic substances occur as groups of similar molecules, such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFAS) and polycyclic aromatic hydrocarbons (PAHs). When possible, guidelines should give options for considering mixtures of chemicals including the use of toxicity equivalency factors, toxic units or total concentrations for congeners within a given class.

2.2 Minimum Data Requirements

The following minimum data set must be present before proceeding with guideline derivation:

- at least one study documenting a marine mammal that has been exposed to the contaminant
- a human health TRV with the associated effect concentration OR at least three acceptable dose-response toxicity studies (*in vivo*) from a mammalian species OR mammal-based point of departure (POD) that is published by an agency and is scientifically credible.

Guideline developers should collect as many lines of evidence as possible to support a WoE approach.

3. CONSIDERATIONS FOR USE

3.1 Guideline Exceedances

CEQGs are predicted no-effect concentrations, representing low-risk conditions, that have been extrapolated from the existing ecotoxicological data sets according to the procedures herein. Therefore, exceeding CEQG values does not necessarily mean adverse effects will occur but suggests further investigation is warranted. Guideline exceedances can be defined in many ways. For example, an exceedance could be based on a single sample, a 30-day average or a certain

magnitude or frequency rate. It is suggested to follow provincial or territorial jurisdictional guidance for your site. Whenever possible, collect sufficient high-quality monitoring data and define an exceedance prior to evaluating the monitoring data for exceedances. Interpretation requires knowledge of the local environment, professional judgement and other lines of evidence to ensure effective decision-making and resource management.

3.2 Deciding Which Guideline to Apply

3.2.1 Different Receptors

This protocol outlines the derivation process for CEQGs$_{mm}$ from PBT substances. However, other guidelines may already exist for these substances based on different protocols to protect various aquatic receptors or terrestrial receptors who feed on aquatic biota (CCME 1995, 1998, 2007; British Columbia Ministry of Environment and Climate Change Strategy [BC ENV] 2019). These guidelines may be appropriate to use depending on the site and species present. For example, CEQGs$_{mm}$ are not appropriate where marine mammals are not present and where the substance is not expected to affect downstream marine mammal habitat.

3.2.2 Different Environmental Compartments

The dietary CEQG, which is the tissue concentration in prey that is predicted to have no effect on apex marine mammals, is the most reliable CEQG produced by this protocol given that tissue concentrations in prey are representative of the average environmental concentrations and given that tissue concentrations have lower uncertainty compared to the modeled water and sediment CEQGs. However, as sampling is more commonly done on abiotic media, the water and sediment CEQGs can be used to assess risks to marine mammals. Care must be taken, however, to ensure that the sampling protocol considers spatial and temporal variations in contaminant concentrations.

It is recommended that all values available (i.e., tissue, sediment, water) be used in close conjunction with each other if monitoring data allows. It is also recommended to use all available metrics when assessing pollution risks and to use other decision-making tools in addition to CEQGs.

3.3 Site-Specific Guidelines or Objectives

This protocol outlines how to derive generic guidelines intended to protect all marine mammals in Canada. However, a site-specific guideline may be appropriate provided that accurate site- and species-specific information is available. For example, the food-web bioaccumulation models can be tailored to the specific site and species of interest by including model inputs specific to that habitat or ecosystem (for examples, see Alava *et al*., 2012). In addition, food intake and body weight information can be used from the species or population of interest rather than using a default value. A site-specific or habitat-specific guideline can be developed when no generic guideline exists for that substance by following the same general procedures outlined in this document or

adapted from an existing generic guideline already developed. Guidelines can also help inform site-specific objectives which, in contrast to guidelines, may consider technological, socioeconomic, or management factors for specific water bodies (BC ENV 2021; CCME 2003; Rao *et al*., 2019).

3.4 Environment Quality Guidelines Below Ambient Concentrations

In some cases, the CEQG may be below the ambient concentrations of a contaminant. This reflects both the historical use of some contaminants and the persistence of these contaminants. It also indicates that current ambient concentrations may be causing adverse health impacts to marine mammals. Efforts should therefore be made to reduce the loading of additional contaminants to marine mammal habitats.

4. COMPILATION OF BACKGROUND INFORMATION

4.1 Literature Search

Comprehensive data on the toxicology of a substance are necessary for the development of CEQGs. Supplementary information on the substance is also reviewed to assist with the development and use of the CEQG. Literature searches should gather the following information:

- production and uses
- physical and chemical properties
- sources to aquatic environments
- environmental concentrations
- methods of quantification and current detection limits
- environmental fate, behaviour and persistence
- solubility of the substance in the various aquatic environments (freshwater and marine, hard versus soft water, pH and temperature influence, and so on)
- mobility of the substance and the compartments of the aquatic environment in which it is most likely to be present
- kinds of chemical and biological reactions that take place during transport and after deposit
- eventual chemical form under various environmental conditions
- persistence of the substance in water, sediment and biota
- toxic interactions with other substances (i.e., parameters affecting exposure and toxicity)
- bioaccumulation and biomagnification potential
- toxicokinetics and toxicodynamics
- mode of action.

For some chemicals there may be a lack of information regarding environmental fate and biological consequences (e.g., mode of action). If no information is available on some of the above topics, this should also be noted in the technical document.

4.2 Environmental Concentrations

Whenever possible, information on the environmental concentrations of the substance in sediment, water and tissues from the three oceans bordering Canada should be summarized. This information can be taken from the scientific literature and government reports. Where possible, spatial and temporal variation should be noted to provide a full picture of trends and geographical distribution of the substance.

It is important to recognize the influence of method detection limits (MDLs), sampling methodology and analytical methods when characterizing environmental concentrations. The MDL is defined as "the minimum concentration of a substance that can be measured and reported with 99% confidence that the analyte concentration is greater than zero and is determined from analysis of a sample in a given matrix containing the analyte" (Code of Federal Regulations [CFR] 2011). MDLs have typically decreased over time and historical results, reported as equal to or half of the MDL, may lead to a misinterpretation of the data. Clear documentation should be provided to describe how historical MDLs and outliers were treated in the analysis. Additionally, sampling methodology and analytical methods will influence the final concentrations. Documenting these methods will allow due appropriate consideration when making temporal or spatial comparisons.

For chemical mixtures such as PCBs and PBDEs, the specific congeners measured should be noted. Comparisons across studies where chemical concentrations are expressed as the sum of a chemical class, for example ΣPCBs, can be hindered by having a different sub-set of congeners. Congeners can differ in toxicity and for some congeners, toxicity may not be known. A more robust comparison can be made if the congener subset is documented.

4.3 Analytical Methods

A description of the analytical methods for substance quantification in environmental samples should be included in the technical report. Any discrepancies between substance quantification over the years (i.e., outdated methods) and differences between measurements in the lab vs the field should be discussed. It is necessary to consider the MDL of the recommended analytical method. Many organic chemicals require specialized high-resolution methods to detect levels found in the ambient environment. These are often more costly than standard methods but are necessary to quantify the concentrations of these chemicals. Some chemical groups are composed of multiple congeners (e.g., PCBs, PBDEs); reporting the chemical concentrations in environmental media should identify individual congeners whenever possible.

4.4 Bioaccumulation Factors

Bioaccumulation factors are necessary bioaccumulation metrics for calculating the Canadian water quality guideline for the protection of marine mammals ($CWQG_{mm}$) and the Canadian sediment quality guideline for the protection of marine mammals ($CSeQG_{mm}$) once the concentration in the biota or prey tissue has been determined. Bioaccumulation factors are obtained from the literature and can consider empirical data (i.e., field- or laboratory-derived estimates) and predicted data

from food web bioaccumulation models. The BAFs must be scientifically defensible and, whenever possible, represent the conditions found in the three oceans bordering Canada.

4.5 Mode of Toxic Action

Information on the mode of toxic action (MoA) should be included to better understand how the substance may affect the health endpoints of marine mammals (e.g., leading to immunotoxicity, endocrine disruption, neurotoxicity and carcinogenesis). This review should extend across mammalian species to identify endpoints that are biologically relevant to marine mammals. This is especially important when data from laboratory animals are used to extrapolate the effects to marine mammals. Many resources are available to help establish MoA, such as adverse outcome pathways (AOP), key characteristics (KCs) frameworks, quantitative structure-activity relationships (QSARs) and databases (e.g., EnviroTox).

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5. DERIVATION OF A TOXICITY REFERENCE VALUE FOR MARINE MAMMALS

5.1 What Is a Toxicity Reference Value and How Is It Derived?

A TRV is a parameter used to quantitatively assess potential risks to human health that are associated with exposure to a chemical or contaminant of concern (Health Canada 2021b). TRVs are published by various national and international agencies to characterize substance toxicity. They can be derived by dividing the POD, which is the point in a toxicological dose-response data set that generally corresponds to an estimated low- or no-effect level, by an uncertainty factor (UF). UFs, also known as safety factors or assessment factors, are numerical factors applied to the lowest value from an empirical toxicological data set for a given substance to account for various uncertainties (Okonski *et al.* 2021).

Dose-response data for marine mammals are rarely available given the ethical, legal and logistical constraints required to obtain them. Therefore, human health TRVs, which are extrapolated from laboratory animal data sets (e.g., rats, mice, mink) (CCME 1998; United States Environmental Protection Agency [US EPA] 2014), should be used as a starting point for selecting a POD. Interspecies extrapolation is a process frequently used in human health risk assessment. Ross (2000) and Ross and Birnbaum (2003) highlight the need for a WoE approach in marine mammals, whereby the extrapolation of data from non-marine mammalian species to marine mammals is appropriate owing to the similarities in physiological systems and mechanisms of toxicity among

mammals, the lack of controlled studies to determine effects thresholds for marine mammals, and similar protection goals (protection of the individual) for humans and marine mammals. Thus, like human risk assessment, it is reasonable to use the most conservative toxicity thresholds among available mammalian studies when deriving TRVs for apex marine mammals.

If there is, however, evidence to suggest that an alternate endpoint is preferred given the physiological, behavioural, ecological, and genetic or interspecies differences between marine mammals and humans, then an alternate POD may be selected from the prepared database.

5.2 Selection of a Point of Departure

Two approaches are available for selecting a POD. The first, and most preferred, approach is to use an existing POD from a human health TRV. If a human health TRV and corresponding POD are not available or deemed inappropriate, a POD can be determined from a literature review.

5.2.1. Selection of an Existing Point of Departure

If available, human health TRVs can be used as a starting point for selecting a POD and associated UFs for calculating a TRV for marine mammals (see Figure 1). Based on a toxicological dose-response data set, a POD is identified as either a no- or low-effect level. Multiple endpoints may be present in a toxicological data set (e.g., a benchmark dose lower confidence limit [BMDL][1], a no observed adverse effect level [NOAEL], a lowest observed adverse effect level [LOAEL], or a maximum acceptable toxicant concentration [MATC]) and the selected POD is generally the lowest value among these four endpoints. Human health TRVs[2] should be compiled from various health agencies, including, but not limited to, Health Canada, the US EPA, California Environmental Protection Agency, the World Health Organization, the Agency for Toxic Substances and Disease Registry (ATSDR), the European Food Safety Authority and the International Programme on Chemical Safety. If multiple human health TRVs are available, then scientific judgement should be used to select the most appropriate one.

5.2.2. Determination of a Point of Departure from Laboratory Dose-Response Data

If a human health TRV and its corresponding POD is unavailable or deemed inappropriate, a POD may be derived from the literature (Figure 1). This will involve collating and reviewing dose-response toxicity data on surrogate mammals using the criteria for data quality described in Appendix A. Once a toxicity database has been compiled, a POD is selected, which is generally the most sensitive endpoint. Effects not previously noted in marine mammal studies may be available in laboratory studies. However, given the similarities in mechanisms of toxicity across mammals, these endpoints should not be discounted without justification. The selection of the final POD should be done with the protection goal in mind, i.e., to be protective of individual marine mammals.

[1] The benchmark dose (BMD, or its lower confidence limit, BMDL) is a dose that produces a predetermined change in the response rate of an adverse effect (e.g., 1%, 5% or 10% of response compared to control, depending on the severity of the endpoint) and is obtained by fitting dose-response data with mathematical models.

[2] Terminology may vary depending on the agency (e.g., tolerable daily intake (TDI), reference dose (RfD), minimal risk level (MRL)).

5.2.3. Marine Mammal Biomonitoring Studies

Marine mammal contaminant data, biomarker studies and meta-analyses that identify tissue residue concentrations and the related physiological endpoints should be summarized. Although the correlation in biomarker studies cannot be used to infer causality given the potential effects of other factors, including exposure to other chemicals (chemical mixtures), several studies systematically collated together can be used in a WoE approach to support the calculated CEQGs.

5.3 Selection of Uncertainty Factors

The UF is used to account for sources of uncertainty that cannot be estimated from the data set, such as intraspecies variability including sensitive sub-populations, interspecies variability including differences in toxicodynamics and toxicokinetics, and data quality and quantity. Maximum UFs for each category are typically set at 10, though lower numbers are commonly used and applied in a multiplicative manner (Stedeford *et al.* 2007). Toxicology data sets involving well studied chemicals, marine mammals and sensitive endpoints may rely on fewer UFs or none at all. Scientific judgement should be used to select an appropriate UF, and the rationale must be documented. If more than one UF is needed, the selection of their values should be assessed collectively rather than in isolation from the others.

5.3.1. Intraspecies Variability

To some degree, the BMF will account for the intraspecies uncertainty due to different life stages, as all life stages are considered in the individual-based model (IBM) and the most sensitive life stage is selected for the BMF (see Section 6.2). However, if evidence suggests that an additional UF is warranted, the value should not exceed 10.

5.3.2. Interspecies Variability

While allometric scaling of acute toxicity data may be warranted to account for interspecies differences, there is no evidence to support it for extrapolation of chronic toxicity data (Sample and Arenal 1999). Its use has therefore been discouraged for extrapolating chronic endpoints across species (Allard *et al.* 2010; Government of Canada 2013). Interspecies scaling is done by using the ratio of food intake to body weight. If adequate scientific rationale exists to include a further UF for interspecies extrapolation, then it should not exceed 10.

5.3.3. Data Quality and Quantity

Most agencies recommend the use of a UF to account for deficiencies in the toxicological data set. Given that the original assessor will have the best understanding of the data set, the original UF for data deficiency should be retained if a POD from a human health TRV is used. If a new database

is collated, the criteria in Appendix A should be used to assess the UF selection for toxicity database deficiencies.

5.4 Calculation of the Marine Mammal Toxicity Reference Value

The selected POD, which is commonly reported as an oral dosage in food, must be adjusted to a daily intake rate by including the body weight (bw in kg) and daily food ingestion (g per day) of the test animal (see Equation 1).

Equation 1. $$\text{PODdi} = \frac{\left[\left(\frac{\text{mg chemical}}{\text{kg food}}\right)\times\left(\frac{\text{g food}}{\text{d}}\right)\times\frac{1\text{ kg}}{1{,}000\text{ g}}\right]}{\text{kg bw}}$$

where:

PODdi = POD converted to daily intake in $mg \cdot kg^{-1}$ bw per day
POD = selected NOAEL, BMDL or other endpoint reported as mg chemical·$kg\ food^{-1}$
bw = body weight in kg
d = day

Body weights and daily food ingestion, on a wet-weight basis, should be used from the toxicity study from which the daily oral dose is reported. If these values are not available from the study, they may be obtained from the literature (e.g., Banfield 1974; Dunning 1993; National Institute for Occupational Safety and Health [NIOSH] 1993).

The final TRV is then calculated as:

Equation 2. $$\text{TRV} = \frac{\text{POD}}{\text{UF}_1\times\text{UF}_2\times\ldots\times\text{UF}_X}$$

where:

TRV = tolerable daily intake ($mg \cdot kg^{-1}$ bw per day)
POD = selected NOAEL, BMDL or other endpoint adjusted to a daily intake rate in Equation 1 and reported in $mg \cdot kg^{-1}$ bw per day
UF = product of the uncertainty factors

5.5 Consideration of Carcinogenic Effects

Marine mammals exposed to carcinogenic pollutants are at risk of developing cancer over their lifetime (Gulland *et al.* 2020; Newman and Smith 2006; Randhawa *et al.* 2015). The prevalence of cancer in marine mammals chronically exposed to persistent organic pollutants (POPs) has been reported for free-ranging populations (e.g., SRKW and SLEB) inhabiting highly contaminated marine regions in the Northeastern Pacific Ocean and St. Lawrence Estuary (Gulland *et al.* 2020; Randhawa *et al.* 2015; Raverty *et al.* 2020). As this protocol is concerned with protecting individual marine mammals rather than populations, it is important to consider the carcinogenic

effects of the substance. As mentioned in Section 5.1, TRVs for non-cancer effects are determined based on the threshold below which no adverse effects are expected. In cases where sufficient data are available to demonstrate the occurrence of a threshold for cancer, the same procedure (POD divided by a global UF) can be used to derive a TRV for cancer. Otherwise, by default, it is assumed that any level of exposure to a carcinogenic substance is associated with a risk or probability of developing cancer.

The corresponding TRV refers to a cancer slope factor (CSF,[3] expressed in $mg \cdot kg^{-1}$ bw per day), which can be converted into a risk-specific dose (RSD[4], expressed in $mg \cdot kg^{-1}$ bw per day), as a dose corresponding to a given incremental risk. In the context of guideline derivation, the incremental risk is directly related to the protection objective (i.e., the incremental risk associated with the guideline shall be deemed negligible or acceptable). For instance, in its guidance for federal contaminated sites, Health Canada (2021a) considers that an incremental risk of 10^{-5} (one in 100,000) is essentially negligible for humans, and in the United States, an incremental risk of 10^{-6} (one in 1,000,000) is retained as a regional screening value for potentially carcinogenic chemicals (US EPA n.d.). To put these incremental risk values in perspective, the Canadian Cancer Society estimates that four in 10 Canadians (risk of 0.4) are expected to develop cancer during their lifetime (Canadian Cancer Society n.d.).

6. ESTIMATING CONCENTRATIONS IN OTHER ENVIRONMENTAL MEDIA

6.1. Overview

Once the TRV has been established, empirical data or toxicokinetics (food web) bioaccumulation models can be used to relate the TRV to the associated concentrations in prey tissue, water and sediment. Protective prey tissue concentrations are derived by dividing the TRV by a BMF which accounts for the biomagnification of the chemical in the marine mammal. Water concentrations are calculated by dividing the concentration in the biota or prey tissue by a BAF and sediment guidelines are derived by dividing the concentration in biota or the prey tissue by a biota-sediment accumulation factor (BSAF) or by modelling the concentration in water and sediment using the chemical properties of the substance (e.g., the fugacity ratio or equilibrium partitioning method). This suite of bioaccumulation metric factors (i.e., BMF, BAF, BSAF) can be derived using field-based or food web modelling approaches, or both. However, the uncertainty associated with calculating the guidelines increases when moving away from the TRV. Thus, the uncertainty associated with the sediment and water guidelines will be greater than the tissue diet guideline (see Figure 2).

[3] The CSF is a measurement of risk. It corresponds to the risk of developing cancer associated with a lifetime average exposure dose of 1 $mg \cdot kg^{-1}$ bw per day (e.g., a CSF of 0.2 [$mg \cdot kg^{-1}$ bw per day] means that lifetime average exposure to 1 $mg \cdot kg^{-1}$ bw per day may result in the development of cancer in one out of five individuals (a probability of 0.2, or 20%) exposed under these conditions.

[4] The RSD is the dose associated with a given risk (probability) of developing cancer. For instance, a dose associated to a risk of 10^{-5} (i.e., a 10^{-5} RSD) of 0.00005 $mg \cdot kg^{-1}$ bw per day means that one out of 100,000 individuals (risk or probability of 10^{-5}, i.e., 0.00001 or 0.001%) exposed over their lifetime to this average dose may develop cancer due to this substance. RSD $= \frac{CSF}{10^{-5}}$

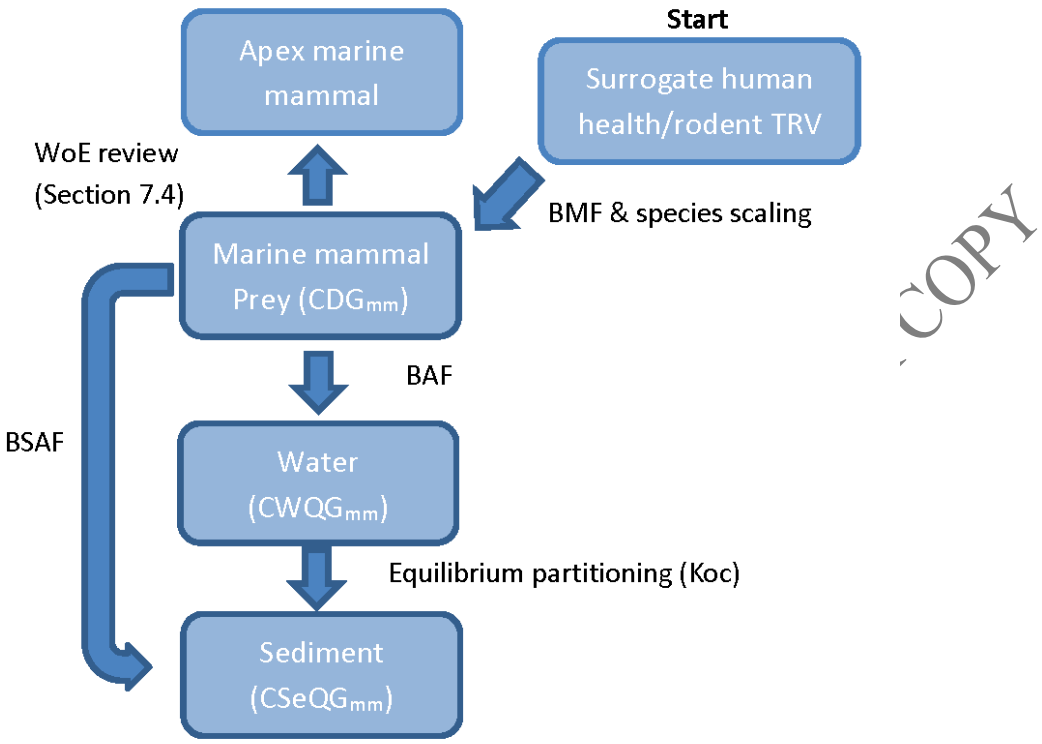

Figure 2. Pathways for the Derivation of Environmental Quality Guidelines for Prey Tissue, Water and Sediment Starting with a Surrogate Toxicity Reference Value

Notes:
BAF = bioaccumulation factor; BMF = biomagnification factor; BSAF = biota-sediment accumulation factor; CDG_{mm} = Canadian dietary guideline for the tissue of marine mammal prey; $CSeQG_{mm}$ = Canadian sediment quality guideline for the protection of marine mammals; $CWQG_{mm}$ = water quality guideline for the protection of marine mammals; K_{OC} = organic carbon-water partition coefficient; TRV = toxicity reference value; WoE = weight-of-evidence.

6.2. Biomagnification Factor—Marine Mammal to Prey

A BMF is the ratio of the chemical concentration in the tissue of a predator to the chemical concentration in the tissue of the prey at the next lowest trophic level (Gobas *et al.* 2009; US EPA 2000). The ratio is unitless. For non-ionic chemicals and specific ionic chemicals with high Kow values, the concentrations should be lipid-normalized.[5]

BMFs are used to estimate the prey tissue concentration that will be protective of marine mammals. The BMF estimates the concentration in marine mammal tissue that will occur after generations of exposure to the contaminant. In marine mammals the body burden of contaminants accumulates over a lifetime of exposure and calves are exposed to contaminants by way of placental and lactational transfer (Barrett *et al.* 2021; Desforges *et al.* 2012; Lee *et al.* 2023). Although laboratory feeding studies selected as the POD are typically chronic exposures, these are often for less than

[5] Note that at the time of publication, lipid-normalized BMFs cannot be applied to per- and polyfluoroalkyl substances (PFAS) as these ionic substances mainly bond to the protein content or fraction of animal tissues.

one year and do not account for the long lifespans of marine mammals or for maternal transfer exposures.

BMFs can be estimated from ecological models or field data, and these can be used together, as modelled BMFs are often compared to field data for validation. If field-derived BMFs are available, they can be considered in a WoE approach. Field-derived BMFs, based on empirical tissue samples collected from predator and prey, can provide valuable estimates for guideline derivation. However, the process of calculating field-derived BMFs comes with several uncertainties and limitations, including high cost, lengthy time, legal restrictions and ethical implications when working with threatened and endangered species. Due to sampling restrictions, available data are limited to dart-biopsy (blubber tissue) sampling from free-ranging (wild) marine mammals, if official authorized licence allows, or tissue samples opportunistically collected from stranded animals or from subsistence harvests by Indigenous communities. As such, they may not necessarily represent all life stages or health conditions present in the population.

For this protocol, it is recommended to use BMFs calculated using the IBM developed by Hickie and others (Hickie *et al.* 2000; 2005; 2007; 2013). A major advantage of this model is that it does not rely on ecosystem-specific input values, such as the contaminant concentration in fish, to calculate a BMF for a specific species and substance. This allows the output of the models to be applied to a wide range of contaminants without prior knowledge of concentrations in ecosystem compartments. The IBM has been parameterized for three apex marine mammal species in Canada: beluga whale (Hickie *et al.* 2000), killer whale (Hickie *et al.* 2007) and ringed seal (Hickie *et al.* 2005) which represent, respectively, the Atlantic, Pacific and Arctic oceans in Canada.

The IBM reconstructs temporal trends in marine mammals by considering the toxicokinetics of the marine mammal (e.g., uptake, distribution, elimination) and life history characteristics and calculates the tissue concentration in the marine mammal at specific time intervals over its lifespan, including the contaminant burden of offspring due to placenta transfer and nursing. The model loops upon itself until the contaminant concentrations reach a steady state. In this way, the model presents a multi-generation scenario (Hickie *et al.* 2007). The model produces multiple predicted BMFs for each sub-population (i.e., time-dependent for calves or pups, juveniles, adult females and adult males) for the three species. The mean calf or pup value was selected to be protective of each respective species.

For this protocol, the overall mean calf or pup BMF for killer whales, beluga whales and Arctic ringed seals was chosen as a surrogate for marine mammal BMF (see Table 1). These marine species were chosen as surrogates for the other species of apex marine mammals representative of the three oceans bordering Canada, to which was applied the most recent bioaccumulation IBM that includes K_{OW}-dependent terms. When considering life history traits, the selection of the killer whale is a suitable surrogate given that orca whales have the longest birth intervals (five years for killer whales versus three years for beluga whales and one year for ringed seals). This means orca females have the longest period to accumulate a contaminant burden between births, which is then transferred to the orca calf via maternal transfer. Further, seals are known to have a greater capacity to biotransform organic chemicals such as PCBs, which leads them to having lower BMFs.

Kow-specific equations were estimated from field data for PCBs for uptake efficiency from prey (McLachlan 1994) and partitioning to the milk (Cadieux *et al.* 2016). Field data for PCBs and PBDEs were used to estimate Kow-specific equations for partitioning to the fetus (Desforges *et al.* 2012). These biological processes (i.e., digestion, gestation and lactation) are not the result of simple equilibrium partitioning. They require multiple steps, which occur in both aqueous and lipid states. Therefore, contrary to the positive relationship between Kow and concentration in lipids, there is an inverse relationship between Kow and uptake efficiency, partitioning to fetus and partitioning to the milk (Cadieux *et al.* 2016; Desforges *et al.* 2012; McLachlan 1994). These relationships have not been tested for other POPs but, aside from PFAS that accumulates in proteins, it is anticipated that they will be similar across other lipophilic contaminants (Hickie pers. com. 2023).

Table 1. Mean Calf or Pup BMFs (Wet-Weight-Based) for a Range of Kow Values

Log Kow	Arctic ringed seals (*Pusa hispida*)	Beluga whales (*Delphinapterus leucas*)	Killer whales (*Orcinus orca*)
5	271	719	909
5.2	271	722	910
5.4	271	722	910
5.6	275	718	903
5.8	272	711	894
6	265	699	879
6.2	255	680	857
6.4	241	654	825
6.6	224	617	779
6.8	201	569	714
7	179	504	630
7.2	149	425	524
7.4	117	334	404
7.6	85	242	285
7.8	55	159	181
8.0	33	95	104

Log K_{OW}	Arctic ringed seals (*Pusa hispida*)	Beluga whales (*Delphinapterus leucas*)	Killer whales (*Orcinus orca*)
8.2	17	52	55
8.4	8.5	27	28

Notes
BMFs were estimated using the IBM (Hickie *et al.*, 2000; 2005; 2007; 2013) that was updated to include K_{OW}-specific equations for contaminant assimilation from prey and contaminant partitioning to milk and fetus. Input values for the IB model are given in Appendix B. The input values include the assumption of negligible rates of biotransformation.

6.3. Bioaccumulation Factor—Prey to Water

The BAF is the ratio of contaminant concentration in the tissue of an organism (e.g., aquatic biota or the prey of marine mammals) to the contaminant concentration in water or the aquatic environment (Gobas *et al.* 2009) expressed in units of L·kg tissue on a wet-, dry- or lipid-weight basis. The BAF approach is predicated on the following assumptions: both the organism and its food are exposed to the same concentration of contaminant in the water and the exposure concentration does not change substantially over time (i.e., steady state). Depending on the type of chemical and its properties, BAFs can be measured or predicted using one or more of the following methods:

- Measured BAFs derived from data obtained from a field study (i.e., field-measured BAFs, or trophic magnification factors [TMFs])
- BAFs derived from laboratory measurements
- Predicted BAFs from models (e.g., AQUAWEB).

Field studies should be reviewed to ensure that the substance under investigation has reached a steady state in the aquatic ecosystem or that water concentrations were averaged over a duration that is comparable to the time required for the substance to reach a steady state (US EPA, 2000). Further, the study should be examined to ensure the aqueous concentrations were measured accurately, especially in older studies where cross-contamination may have artificially increased BAF values (Borga *et al.* 2005).

The selection of a BAF involves collating literature values and selecting a value that is representative of each of the ocean regions where differences are noted. The final value selected will be the most conservative of the values to ensure the final CEQGs ($CEQGs_{mm}$) are protective for all apex marine mammal predators.

TMFs represent the "diet-weighted average BMF of chemical residues across food webs" (Burkhard *et al.* 2013). They are typically derived from the anti-log of the regression slope of the log of lipid-normalized chemical concentrations in organisms versus a spanning range of species trophic levels, which are determined from stable isotope (δ^{15} N) data (Borga *et al.* 2012). A recent review by Kidd *et al.* (2019) provides practical guidance on TMF use and selection for environmental quality guideline derivation, including considering the following criteria when determining the reliability of TMF estimates:

- a minimum of two or three trophic levels
- measured contaminant concentrations in whole organisms
- lipid-normalizing concentrations of organic contaminants
- the inclusion of several lower trophic level invertebrate taxa (e.g., zooplankton, benthic invertebrates)
- a balanced number of samples across trophic levels
- adequate and balanced samples for each trophic level
- the inclusion of organisms known to be linked by diet through the food web
- measured contaminant concentrations above detection limits in all samples
- all sampled organisms collected within a similar time frame (e.g., one season)
- caution for potential upward bias of TMF estimates if homeotherms and air-breathing organisms (i.e., birds and mammals) are included in the data set.

If using TMFs, the final step is to estimate the BAF of the contaminant from water to plankton. Chemical-specific information for the BAF (either laboratory or field measurements) is preferable to assuming equilibrium, but if no chemical-specific information is available then the equilibrium approach is acceptable. The final BAF for prey to water will then be the product of the $TMF_{prey:plankton}$ and the $BAF_{plankton:water}$:

Equation 3. $BAF_{prey:water} = [TMF_{prey:plankton}] \times [BAF_{plankton:water}]$

6.4. Estimating Sediment Concentrations

Sediment concentrations can be estimated in two ways: either using the equilibrium partitioning approach, which estimates the bulk sediment concentration from the water concentration based on the organic carbon-water partition coefficient (K_{OC}) (DiToro *et al.* 1991), or by using the BSAF, which is the ratio of the contaminant concentration in the tissue (on a wet-weight or lipid-normalized basis) of an organism to the contaminant concentration in the sediment (on a dry-weight basis or a total organic carbon (TOC) content-normalized basis) (Alava *et al.* 2012; Arblaster *et al.* 2015). Each of these methods are described in this section.

The equilibrium partitioning approach is applicable to non-ionic organic chemicals and assumes that the concentration between the organic carbon content of the sediment and the sediment pore water are in equilibrium (Di Toro *et al.* 1991). If the concentration in the water is known, an estimate of the concentration in sediment organic carbon can be calculated using the organic carbon-water partitioning coefficient and the percentage of organic carbon in the sediment.

Alternatively, a BSAF can be used to back-calculate the concentration in the sediment given a known concentration in a biota. A BSAF can be measured either in the laboratory or in the field. Field measurements done on migratory or wide-ranging species can add challenges, as contaminants can be accumulated from other locations. BSAFs are most applicable to site-specific assessments using sessile organisms. However, this bioaccumulation metric has been applied to marine mammals (e.g., southern resident killer whales) and their critical habitat (e.g., Alava *et al.* 2012; Arblaster *et al.* 2015; Lachmuth *et al.* 2010) and has the advantage of integrating biological processes not considered in the equilibrium approach. Like BAFs, a review is necessary to ensure

that the aquatic ecosystem is at equilibrium and that the appropriate analytical methods were used to prevent cross-contamination.

The BSAF is calculated as:

Equation 4. $$\text{BSAF} = \frac{C_t}{C_s}$$

where:

BSAF = the biota-sediment accumulation factor
Ct = concentration of chemical in the biota species ($g \cdot kg^{-1}$ wet weight)
Cs = concentration of contaminant in the sediment ($g \cdot kg^{-1}$ dry weight) (Alava *et al.* 2012; Arblaster *et al.* 2015)

The BSAF can also be normalized in terms of lipid content and TOC fraction in the sediment, and the resulting units for Ct and Cs become $g \cdot kg^{-1}$ lipid in biota and $g \cdot kg^{-1}$ organic carbon [OC] in sediment, respectively (Alava *et al.* 2012; Arblaster *et al.* 2015).

Whenever possible, BSAFs should be used over the equilibrium approach. If using the BSAF approach, values should be collated for the three oceans bordering Canada. If BSAFs are not available for all three oceans and uncertainty exists as to its application to the remaining oceans, then the lower value of the two approaches (equilibrium partitioning vs BSAF) should be chosen.

6.5. Criteria for Other Models

It is possible that a model other than the IBM or AQUAWEB—applied for BMF and BAF predictions, respectively—may be required due to properties of the contaminant. In these situations, the model selected should meet the following criteria:

- The model is well established and cited in the peer-reviewed literature.
- Code and equations are transparent and publicly available.
- Chemical or physical properties of the chemical are explicitly included in the model or are available from a reputable source, including:
    - K_{OW}
    - Octanol-air partition coefficient (K_{OA})
    - Sediment-to-water concentration ratio
- Site-specific environmental parameters of the ecosystem are assessed, including:
    - mean water temperature
    - concentration of particulate organic carbon in the water
    - concentration of dissolved organic carbon in the water
    - concentration of suspended solids in the water
    - organic carbon content of the sediment (TOC content)
    - chemical concentration in the water
    - chemical concentration in the sediment (water temperature, salinity, pH)
- There is a sufficient quantity and quality of contaminant data for abiotic compartments (sediment and water).

- There is a reliable understanding of the composition and structure of the food web and dietary preferences of organisms.
- Site-specific biological properties and life history characteristics of biota are included (organism lipid content, dietary uptake rate, growth rate, organism wet weight or volume, diet percentage or organism feeding preferences).
- Empirical data are available for biota (upper trophic level or apex predators) to test the performance of the model (model bias).

Food web bioaccumulation models meeting these modelling criteria are available and have been developed and applied for marine regions and ecosystems of the Northeastern Pacific, including British Columbia (Canada) and San Francisco Bay (California, United States) [see the supporting or supplementary information data sets published in Alava *et al.* 2012; Alava *et al.* 2016; Gobas and Arnot 2010].

7. CALCULATION OF THE FINAL CANADIAN ENVIRONMENTAL QUALITY GUIDELINES

7.1. Dietary Guideline

The Canadian dietary guideline (CDG_{mm}) for the tissue of marine mammal prey is an expected tissue residue concentration to be protective of apex marine mammals. When using field data or species-specific models for the species deemed to be most sensitive, resulting BMFs may be used directly to determine the CDG_{mm}. The rate of food intake to body weight (FI:BW) for the species-specific BMF is used to convert the daily dietary dose to a dietary tissue concentration (CCME 1998) [see Equation 5]. In Appendix B, Table 3 provides a list of FI:BW rates for the mammalian species from Table 1.

The CDG_{mm} is calculated using the following equation:

Equation 5. $$CDG_{mm} = \left(\frac{TRV}{(FI:BW) \times BMF}\right)$$

where:

CDG_{mm} = the Canadian dietary guideline protective of marine mammals ($mg \cdot kg^{-1}$ wet weight diet)
TRV = toxicity reference value established in Section 5 ($mg \cdot kg^{-1}$ bw per day)
FI:BW = ratio of food intake (kg wet weight diet per day) to body weight (kg bw) for the same species as the selected BMF
BMF = biomagnification factor established in Section 6.2 (unitless)

7.2. Water Quality Guideline

The $CWQG_{mm}$ is calculated using the following equation:

Equation 6. $$CWQG_{mm} = \frac{CDG_{mm}}{BAFprey:water}$$

where:

$CWQG_{mm}$ = Canadian water quality guideline protective of marine mammals ($mg \cdot L^{-1}$)
CDG_{mm} = Canadian dietary guideline established in Section 7.1. ($mg \cdot kg^{-1}$ wet weight)
$BAF_{prey:water}$ = bioaccumulation factor established in Section 6.3 ($L \cdot kg^{-1}$ wet weight)

7.3. Sediment Quality Guideline

The $CSeQG_{mm}$ can be calculated using the equilibrium partitioning approach (DiToro *et al.* 1991) or using the BSAF (Alava *et al.* 2012; Arblaster *et al.* 2015). See Section 6.4 for a discussion of these approaches.

Sediment concentrations can be calculated with the equilibrium partitioning approach using the following equation:

Equation 7. $$CSeQG_{mm} = CWQG_{mm} \times K_{oc} \times \%OC$$

where:

$CSeQG_{mm}$ = Canadian sediment quality guideline protective of marine mammals ($mg \cdot kg^{-1}$ dry weight sediment)
$CWQG_{mm}$ = Canadian water quality guideline protective of marine mammals ($mg \cdot L^{-1}$)
K_{OC} = organic carbon-water partition coefficient for the substance ($L \cdot kg^{-1}$)
% OC = percentage of organic carbon adjustment (typically to 1% to provide a conservative benchmark against which to compare monitoring data)

Before making comparisons to the $CSeQG_{mm}$, monitoring data must be normalized to 1% OC to assess whether the guideline value is exceeded.

The following equation can be used to calculate the $CSeQG_{mm}$ using the BSAF (adapted from Alava *et al.* 2012; Arblaster *et al.* 2015):

Equation 8. $$CSeQG_{mm} = \frac{CDG_{mm}}{BSAF}$$

where:

$CSeQG_{mm}$ = Canadian sediment quality guideline protective of marine mammals ($mg \cdot kg^{-1}$ sediment)
CDG_{mm} = Canadian dietary guideline established in Section 7.1 ($mg \cdot kg^{-1}$ wet weight diet)

BSAF = biota-sediment accumulation factor (kg OC sediment/kg lipid biota or kg dry weight sediment/kg wet weight biota)

7.4. Weight-of-Evidence Review

A WoE approach is generally understood as a method for decision-making that involves consideration of multiple sources of information and lines of evidence. A WoE framework has been espoused for marine mammals, where cause-and-effect studies are lacking and extrapolation from other mammals (e.g., lab rodents) offers a resolution to such information gaps (Ross 2000). A WoE approach avoids relying solely on any one piece of information or line of evidence. A WoE approach may be applied at various stages of guideline development. It can be used to evaluate the quality of a single study, to assess similar studies for a particular parameter or endpoint, or to integrate information across multiple lines of evidence to support the choice of the $CEQG_{mm}$. If it is not possible to follow the steps outlined in this protocol, a WoE review should be completed that outlines all the lines of evidence compiled and considered that lead to the $CEQG_{mm}$.

Contaminant data from marine mammals is one line of evidence that can be used to assess the calculated guidelines. Although field studies cannot establish a clear causal effect given the presence of other contaminants and stressors, correlations between marine mammal tissue concentrations and a variety of effects (hormone levels, genetic markers, immunological endpoints and blood chemistry; or population-level data such as pregnancy failure, lower birth rate, decreased survivability and population decrease) together with observations from captive feeding studies do strongly suggest a relationship (e.g., Mos *et al.* 2010). The BMF values can be used to predict the concentration in blubber if marine mammals are exposed to the chemical concentration equal to the CDG_{mm}. Ideally, the CDG_{mm} would predict a biomonitored concentration lower than that found in the marine mammals in which an effect has occurred.

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APPENDICES

Appendix A: Compilation and Evaluation of Toxicity Data

Given the sparsity of data for marine mammals and the desire to protect highly vulnerable individuals, endpoints are not restricted to the survival, reproduction and growth endpoints traditionally used to develop guidelines. All endpoints are accepted if there is scientific evidence available that links the endpoint to an adverse outcome in a mammalian species. Adverse effects could include:

- Systemic toxicity such as to the liver, kidney or general system
- Neurotoxicity evidenced by behavioural differences or brain pathology
- Reproductive toxicity that results in effects on fertility or the ability to reproduce
- Endocrine toxicity that affects organs such as the thyroid gland or circulating concentrations of hormones such as estrogen, testosterone or thyroid hormones
- Developmental toxicity, including effects on the developing fetus or maternal systemic effects that interfere with development
- Immunotoxicity that affects immune system organs such as the spleen and thymus, or general immune function disorders

Acceptable endpoints include omics endpoints if they are anchored through a plausible AOP. An AOP consists of three main components: a molecular initiating event where the substance interacts with the biochemistry of the organism; one or more key events where the alteration in the biochemistry leads to an alteration in cell, tissue or organ functioning; and an identified adverse outcome that has the potential to impair the growth, reproduction and survival of an organism. Using AOPs is an emerging approach, and most AOPs are still under development. It is not necessary to firmly establish each of the key events in the AOP but rather to note that the scientific literature has established a high likelihood that the pathway occurs.

All studies used in the development of a guideline must be evaluated to ensure that acceptable laboratory, field or computational practices were used in the design and execution of the study. The exception is studies previously screened and included in the ATSDR database or evaluated by Health Canada or the US EPA, which can automatically be included with no additional screening. Contamination, sampling procedure, sample preservation, storage, pre-concentration and filtration may all be sources of errors, rendering the task of achieving precision and accuracy complex. A thorough investigation of the data (technique and reliability) must be performed before considering the measured concentrations as acceptable values for a guideline derivation (CCME 2007).

While the evaluation of toxicological data should follow a basic format with certain requirements, scientific judgement is often required for the classification of studies. It is not mandatory for toxicity studies to follow standard design protocols; however, the data must be appropriate with respect to the substance in question. Nonstandard testing procedures can yield usable results and should be evaluated on a case-by-case basis for inclusion in the data set. Since standard protocols for toxicity testing may become outdated, and are not always available or followed, a great deal of variability exists in the quality of published data.

To ensure a consistent scientific evaluation for each substance, the following questions should be used to evaluate the quality of each study for the experimental approaches listed here.

All studies (criteria taken directly from US EPA 2002):

- What was the purpose of the study and is there a clearly delineated hypothesis?
- Is there sufficient description of the protocol, statistical analysis and results to make an evaluation?
- Were the appropriate endpoints assessed in the study? Were the techniques used for the assessment scientifically sound?
- Were appropriate statistical techniques applied for each endpoint? Was the power of the study adequate to detect effects?
- Did the study establish dose-response relationships (e.g., lowest observed adverse effect level [LOAEL], effect concentration affecting 10% of the test organisms [EC10])?
- Is the shape of the dose-response curve consistent with the known toxicokinetics of the test compound?

In vivo laboratory dose-response studies from any mammal (criteria taken directly from US EPA 2002):

- Was the study sufficiently documented (e.g., conducted in accordance with good laboratory practices)?
- Were appropriate analytical techniques used to measure the stability, homogeneity and actual level of the test substance in the study (in the water, feed, air, etc.)?
- Were the dose levels appropriate? What was the basis for choosing the dose levels?
- Was an appropriate method used to assign the animals to the dose groups?
- Was an appropriate route and matrix of exposure employed?
- Was the duration of exposure adequate for the study design?
- Were possible alterations in metabolism considered at the higher exposure levels?
- Does the study demonstrate a clear dose-response relationship? Studies with limited treatment levels may be considered if other toxicological studies support the effect level.
- Does the study report dosage rates (in $mg \cdot kg^{-1} \cdot d^{-1}$), exposure duration, formulation and the administration method used in the study? Dosage rates that have been estimated are acceptable, but measured dosage rates are preferred.
- Was the substance administered in the test via the oral route (i.e., in food, in water or by gavage)? Dietary exposure studies are preferred. Tests using other administration methods (i.e., dermal, respiratory, intravenous, intramuscular, subcutaneous or intra-peritoneal) should not be used unless sufficient supportive information on the pharmacokinetics (absorption, distribution, metabolism and excretion) of the substance was available and the dosage was measured.

In vitro studies (criteria from Emmerich and Harris 2019):

- Does the methodology include all minimum information requirements of the experiment type? If none exist, is information given on buffer (e.g., cell culture medium), lysis conditions, sample preparation, and handling and incubation times?
- Are the sources of all materials (e.g., cells, antibodies, enzymes, proteins, nucleic acids, chemicals) clearly listed, including vendor, catalogue number and lot number?
- For non-commercially-sourced materials, were the necessary quality control analyses conducted to validate their identity, purity, and biological activity?
- Was the source of recombinant proteins reported? This includes the sequence, expression system, purification and analysis for purity and bioactivity.
- Were inhibitors and compounds specifically screened to identify off-target effects?
- Were the methods for purifying and preparing cell lines described?
- Were antibodies screened for specificity and cross-reactivity?
- Did the study design include adequate replication and randomization?
- Was the statistical analysis clearly described and were the corresponding sample size and error bars reported?

In silico studies (criteria from Myatt *et al.* 2018):

- Were all steps and methodologies transparently documented, including the exact software used? (Though not essential, it is best practice for researchers to supply the data and code so the experiment can be replicated.)
- Was the training data set of high quality?
- Did the model have a high prediction reliability?
- Was the selection of structural descriptors biologically meaningful?
- Is there support in the literature for the relationships between structural descriptors and toxicological effect?
- Were the results explained in relation to current toxicological knowledge?
- Were weaknesses in the approach and necessary steps for further validation clearly described?

Appendix B: Individual-based Model Input Values and Rate of Food Intake to Body Weight Estimates

Table B1. Individual-based Model Parameters and Input Values for Orca and Beluga

Time parameters	Orca	Beluga
Years model runs after weaning	68	68
First possible year of pregnancy	15	9
Julian day of copulation	35	35
Julian day of birth	545	455
Julian day of weaning	1278	1,278
Number of days between standard output reports	60	120
Percentage of weaning time calf is in food transition	20	20
Stage-specific food intake multipliers		
Food multiplier for juvenile	1.3	1.3
Food multiplier for adult	1.3	1.3
Food multiplier during pregnancy	1.3	1.3
Food multiplier during lactating	1.3	1.3
Body compartment parameters		
Maximum blubber proportion of body weight	0.29	0.4
Minimum blubber proportion of body weight	0.28	0.4
Fetal blubber proportion of body weight	0.17	0.17
Lipid proportion of blubber, female	0.4	0.8
Lipid proportion of core	0.05	0.05
Ratio of support to fetal mass at term	1	1.0
Nonpregnant base uterus weight	0.05	0.05
Ratio of placental to support mass	0.25	0.25
Female orca growth parameters		
Maximum length parameter	564	365
Gompertz B-value length	0.885	0.8805
Gompertz K-value length	0.27000	0.00044
Maximum weight parameter	2703	680
Gompertz B-value weight	2.7	2.572
Gompertz K-value weight	0.00046	0.00044
Male orca growth parameters		
Maximum length parameter	683	416
Gompertz B-value length	1.08	0.987
Gompertz K-value length	0.1752	0.000375
Maximum weight parameter	5015	995
Gompertz B-value weight	3.3	2.895
Gompertz K-value weight	0.00046	0.000375
Lipid proportion of blubber, male	0.4	0.8

Stage-specific metabolic rate multipliers		
1.5 to 3.0 x BMR for neonate (lact)	4	4
1.5 to 3.0 x BMR for first year	4	4
1.5 to 3.0 x BMR for juvenile	4	4
1.5 to 3.0 x BMR for adult (non-reproductive or male)	4	4
1.5 to 3.0 x BMR for adult (pregnant)	4	4
1.5 to 3.0 x BMR for adult (lactating)	4	4
Energetics parameters		
kcal·kg^{-1} food	1,800	1,778
Digestibility of food	0.82	0.82
kcal required to add 1 kg of core mass	9,100	9,100
kcal required to add 1 kg of blubber mass	9,100	9,100
kcal required to add 1 kg of fetus or uterus mass	9,100	9,100
kcal·kg^{-1} blubber energy density	8,500	8,500
Energy efficiency of blubber mobilization	0.9	0.9
kcal·kg^{-1} of milk energy density	3,325	3,000
Lipid proportion in milk	0.3	0.27
Digestibility of milk	0.9	0.9
Energy efficiency in milk production	0.9	0.9
Contaminant kinetics terms		
log K_{OW} for chemical	6.8	6.8
TOX assimilation from food	0.724	0.724
TOX assimilation from milk	0.9	0.9
Blubber-milk TOX partition coefficient	0.490	0.490
Adult TOX whole-body clearance rate (per day)	0.00009	0.000055
Neonate TOX whole-body clearance rate (per day)	0.00009	0.000055
Placenta effect on mother-fetus partition	0.556	0.556
Diet energy content calculation kcal·kg^{-1} wet weight		
Protein % of wet weight (5,600 kcal·kg^{-1})	20	20
Lipid % of wet weight (9,400 kcal·kg^{-1})	8.0	7.0
Pregnant in years	15, 20, 25, 30, 35, 40	10, 13, 16, 19, 22, 25, 28, 31, 34

Notes
The parameters and input values for orca and beluga in Table B1 are taken from Hickie *et al.* (2007).
Tox assimilation from food equation is given by McLachlan (1994); blubber-milk tox partition coefficient equation is given by Cadieux *et al.* (2016); and placenta effect on mother-fetus partition equation is given by Desforges *et al.* (2012).

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Time parameters	Ringed seal
Years model runs after weaning	25
First possible year of pregnancy	7
Julian day of birth (April 1)	90
Julian day of weaning and copulation	130
Julian day of implantation (August 4)	215
Julian day of moult start	180
Julian day of moult, end	210
Number of days between standard output reports	30
Stage-specific food intake multipliers	
Food multiplier for juvenile	1.3
Food multiplier for adult	1.3
Food multiplier during moult	0.7
Food multiplier during lactating	0.6
Body compartment parameters	
Maximum blubber proportion of body weight	0.4
Minimum blubber proportion of body weight	0.25
Fetal blubber proportion of body weight	0.055
Lipid proportion of blubber	0.8
Lipid proportion of core	0.05
Ratio of support to fetal mass at term	1.0
Nonpregnant base uterus weight	0.05
Ratio of placental to support mass	0.25
Female growth parameters	
Maximum length parameter (cm)	126.85
Gompertz B value	0.3377
Gompertz K value	0.00032
Length (cm) to weight (kg) slope	3.2544
Length (cm) to weight (kg) constant	5.0596
Male growth parameters	
Maximum length parameter (cm)	131.21
Gompertz B value	0.400
Gompertz K value	0.0005
Length (cm) to weight (kg) slope	3.0685
Length (cm) to weight (kg) constant	4.693
Stage-specific metabolic rate multipliers	
1.5 to 4.0 x BMR for neonate (lactation)	1.0
1.5 to 4.0 x BMR for first year	4.0
1.5 to 4.0 x BMR for juvenile	4.0

Stage-specific metabolic rate multipliers (Cont.)	
1.5 to 4.0 x BMR for adult (non-reproductive, male)	4.0
1.5 to 4.0 x BMR for adult (pregnant)	4.0
1.5 to 4.0 x BMR for adult (lactating)	4.0
Metabolic rate modifier for moulting	0.8
Energetics parameters	
kcal·kg^{-1} food	1,684
Digestibility of food	0.82
kcal required to add 1 kg core mass	9,100
kcal required to add 1 kg blubber mass	9,100
kcal required to add 1 kg fetus/uterus mass	9,100
kcal·kg^{-1} blubber energy density	8,500
Energy efficiency of blubber mobilization	0.9
kcal·kg^{-1} milk energy density	4,000
Lipid proportion in milk	0.38
Digestibility of milk	0.9
Energy efficiency in milk production	0.9
Contaminant kinetics terms	
Name of contaminant in this run	K_{OW} trial
log K_{OW} for chemical	6.8
TOX assimilation from food	0.724
TOX assimilation from milk	0.9
Blubber-milk TOX partition coefficient	0.490
Adult TOX whole-body clearance rate (per day)	0.000027
Neonate TOX whole-body clearance rate	0.000027
Placenta effect on mother-fetus partition	0.556
Diet energy content calculation kcal·kg^{-1} wet weight	
Protein percentage of wet weight (5,600 kcal·kg^{-1})	20
Lipid percentage of wet weight (9,400 kcal·kg^{-1})	6.0
Pregnant in years	8, 9, 11, 13, 14, 15, 17, 19, 20, 22, 23

Note
The parameters and input values for ringed seal in Table B2 are taken from Hickie *et al.* (2005).

Table B3. Rates of Food Intake to Body Weigh (Percentage of Body Weight per Day) for Five Subgroups of Arctic Ringed Seals, Beluga Whales and Killer Whales Estimated with the Individual-Based Bioaccumulation Models

	Juveniles	**Adult males** 10 to 60 years	**Adult females**		
			Non-pregnant	Pregnant	Nursing
Arctic ringed seals	8.8 ± 1.2	7.6 ± 0.3	8.3 ± 0.5	8.5 ± 0.6	10.4 ± 1.8
Beluga whales	5.1 ± 0.7	3.5 ± 0.2	3.8 ± 0.1	4.2 ± 0.4	4.8 ± 0.3
Killer whales	3.5 ± 0.8	2.3 ± 0.1	2.7 ± 0.1	2.8 ± 0.1	3.3 ± 0.3

Notes
Juveniles are considered to be from ages 1.2 to 10 years for beluga and 1.0 to 15 years for killer whales. Differences between the two species are primary due to differences in body mass.