Environment and Climate Change Canada
Environnement et Changement climatique Canada

Federal Contaminated Sites Action Plan (FCSAP): Ecological Risk Assessment Guidance

Module 7 :
Default wildlife toxicity reference values recommended for Federal Contaminated Sites

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GLOSSARY

Acceptable effect level (AEL) – The magnitude (or rate) of effects that would be acceptable for a specific measurement endpoint or assessment endpoint. The AEL operationalizes a protection goal.

Acute – Relating to a small increment of time required to elicit an adverse environmental response. With respect to toxicity testing, the term describes tests applied over a short duration, typically less than 10% of an organism's lifespan. Note, however, that some short-term tests may be defined as chronic rather than acute if they are conducted using a sensitive life stage; definitions of acute versus chronic vary widely by jurisdiction.

Allometric scaling – Mathematical calculations used to scale the dose rates of contaminants from one species to another, in relation to proportional changes in body size. Allometric scaling is based on the principle that species sensitivity is a function of basal metabolic rate, which is related to body mass.

Application factor – see *Safety factor*.

Bioaccumulation – The process by which substances accumulate in the tissues of living organisms. Bioaccumulation occurs when the concentration of a contaminant of concern (COC) in an organism is higher than the concentration in the surrounding environment. Most substances bioaccumulate to some extent, whereas few biomagnify.

Biomagnification –The process by which chemical concentrations in plants or animals increase relative to food from transfer through the food web (e.g., predators have greater concentrations of a particular chemical than their prey).

Body Mass – Mass of the entire organism. In everyday usage, mass and "weight" are often used interchangeably, but to be scientifically coherent and in accordance with the International System of Units (SI), this document uses body mass (b.m.) instead of body weight (b.w.).

Bound – An exposure level in a toxicological study that included at least one experimental treatment group other than the control in which no effects were observed and one experimental treatment group in which effects were observed. Bound values are generally preferred over *unbound* values for TRV development.

Chronic – Relating to an extended time duration. In the context of toxicity testing, the term is used to describe tests that expose organisms over a substantial portion of their life cycle, for example more than 10% of the life cycle or throughout a sensitive life stage. Definitions of chronic vary widely.

Concentration-response – The relationship between an effects measure and exposure (measured as concentration) across a range of exposure concentrations.

Critical body residue (CBR) – An internal body or tissue concentration that is associated with a toxicological response in a receptor.

Dose-response – The relationship between an effects measure and exposure (measured as dose) across a range of dose values.

Ecological relevance – The degree to which a type of information used in an ERA (i.e., a measurement endpoint or line of evidence) can be meaningfully extrapolated to the biological scale of interest (i.e., the assessment endpoint).

Ecological risk assessment (ERA) – The process of evaluating the potential adverse effects on non-human organisms, populations or communities in response to human-induced stressors (ie. Chemical contaminants). ERA entails the application of a formal framework, analytical process, or model to estimate the effects of human actions on natural organisms, populations or communities and interprets the significance of those effects in light of the uncertainties identified in each study component.

Effect size – The absolute or relative magnitude of response to a stressor for a *measurement endpoint*.

Extrapolation – Inference or estimation by extending or projecting known information to a domain (spatial, temporal, biological, or chemical) that has not yet been studied. In statistics, extrapolation entails estimation (of a value of a variable outside a known range) from values within a known range and requires an assumption that the estimated value follows logically from the known values.

Extrapolation factor – see *Safety factor*.

Hazard quotient (HQ) – The numerical value of the ratio of an estimated environmental concentration or other exposure measure to a response benchmark. Typically, the response benchmark is a value assumed to be protective of the receptor of concern. HQ values below 1 indicate negligible potential for harm, whereas HQ values above 1 indicate that an adverse response is possible and that more precise or accurate evaluation of risks may be warranted to address uncertainty.

Interpolation – To estimate a value (of a function or series) between two known values. The term can also be applied more generically to the assignment of qualities to members of a group on the basis of observations of other members of the same group. Interpolation requires the underlying assumption that members of a group are similarly influenced by the processes under investigation.

Lowest observed adverse effect level (LOAEL) – Lowest amount, dose, or concentration of an agent, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development or life span in an organism, system, or (sub)population. Methods vary for identifying a LOAEL, but often apply statistical significance as a criterion.

No observed adverse effect level (NOAEL) – An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed organisms or population and the appropriate control; some effects may be produced at this level, but they are not considered to be adverse. Methods for identifying a NOAEL vary, but often apply statistical significance as a criterion.

Point estimate – A single numerical value used to represent the state of a random variable. A point estimate collapses (or ignores) all of the variability and uncertainty associated with a parameter or variable.

Protection goal – A narrative statement that defines the desirable level of protection for a receptor or receptor group (see also *Acceptable effect level*).

Qualitative – Adjective describing an approach that is narrative, referring to the characteristics of something being described, rather than numerical measurement.

Quantitative – Adjective describing an approach that is numerical (applies mathematical scores, probabilities, or parameters) in the derivation or analysis of risk estimates.

Receptor of concern (ROC) – Any non-human individual organism, species, population, community, habitat or ecosystem that is potentially exposed to contaminants of concern and that is considered in an ERA. Identification of an organism as an ROC does not mean that it is being harmed, only that a pathway exists such that there is potential for harm.

Safety factor – Also called an application factor, uncertainty factor, or extrapolation factor. A numerical factor sometimes used in effects assessment and applied to observed endpoints in order to derive an exposure concentration below which adverse effects are unlikely to occur. The factor is applied in the face of uncertainty in order to not underestimate risk. As the quantity and quality of test data increases and their relevance to the organisms of interest improves, the size of the extrapolation factor diminishes. This guidance advises against indiscriminate use of safety factors and recommends other techniques for assessing uncertainty.

Threshold – Dividing line (in units of exposure concentration or dose) between a zone of potential response and a zone of negligible response. Thresholds may be estimated using theory, data, or a combination of both. In nature, thresholds generally do not occur as precise or static entities because of the variations among individuals and environmental factors that influence responses. Therefore, a threshold is usually expressed as a best estimate considered protective of most of the population and often includes a margin of safety in the derivation.

Tissue residue guidelines (TRG) – Regulatory criteria or guidelines that refer to an internal body or tissue concentration in a receptor.

Toxicity – The observation of a chemically-induced physiological or biological response that impairs the health of an organism.

Toxicology – The field of science that explores the relationship between substances of environmental concern and the responses elicited from organisms.

Toxicity reference value (TRV) – An exposure concentration or dose that is not expected to cause an unacceptable level of effect in receptor(s) exposed to the contaminant of potential concern. A TRV is a specific type of *threshold*, as defined above.

Unbound – An exposure level (e.g., a NOAEL) in a toxicological study in which either no effects were observed in any of the experimental treatment groups, or in which effects were observed in all of the experimental treatment groups. See *Bound* values, which are generally preferred over unbound values for TRV development.

Uncertainty factor – see *Safety factor*.

Wildlife – In the context of ERA, the term is generally applied to birds and mammals and is sometimes defined to include reptiles and amphibians. It generally excludes fish and invertebrates.

LIST OF ABBREVIATIONS

AEP	Alberta Environment and Parks
BCMOE	British Columbia Ministry of Environment
BM	Body mass
BTAG	Biological Technical Assistance Group (Region 9 of USEPA)
BTEX	Benzene, toluene, ethylbenzene, and xylenes
CBR	Critical body residue
CCME	Canadian Council of Ministers of the Environment
CEAEQ	Centre d'expertise en analyse environnementale du Québec (Québec centre of expertise in environmental analysis)
COPC	Contaminant of potential concern
CWS	Canada-wide standard
DTED	Daily threshold effect dose
EC_x	Effect concentration with *x* percent of organisms affected (e.g., EC_{50})
ERA	Ecological risk assessment
F1 F2 F3 F4	Fractions 1, 2, 3, and 4 of petroleum hydrocarbon mixtures, as defined by CCME (2008), distinguished by number of carbon atoms
FCSAP	Federal Contaminated Sites Action Plan
HMW	High molecular weight
HQ(s)	Hazard quotient(s)
IC_x	Inhibitory concentration
LANL	Los Alamos National Laboratory
LC_x	Lethal concentration to *x* percent of organisms (e.g., LC_{50})
LMW	Low molecular weight
LOAEL	Lowest observed adverse effect level
N/A	None available
N/S	None suitable
NOAEL	No observed adverse effect level
OMOE	Ontario Ministry of Environment
PAH(s)	Polycyclic aromatic hydrocarbon(s)
PCB(s)	Polychlorinated biphenyl(s)
PCDD(s)	Polychlorinated dibenzo-*p*-dioxin(s)

PCDF(s)	Polychlorinated dibenzofuran(s)
PHC(s)	Petroleum hydrocarbon(s)
ROC	Receptor of concern
SD	Standard deviation
TEQ	Toxic equivalency factors
TRV(s)	Toxicity reference value(s)
USEPA	United States Environmental Protection Agency
VOC	Volatile Organic Compounds

PREFACE

The default Federal Contaminated Sites Action Plan (FCSAP) toxicity reference values (TRVs) in this module are not meant to replace TRVs that are selected or derived for site-specific application.

TRVs are used together with site-specific measurements of wildlife exposure as one line of evidence in many ecological risk assessments. However, most ecological risk assessments are based on multiple lines of evidence. Therefore, additional lines of evidence relevant to wildlife, such as observations about presence/absence, density, or other attributes, are also important.

Also, default FCSAP TRVs are not a replacement for Canadian Environmental Quality Guidelines (CEQGs). Default FCSAP TRVs in this module are relevant for wildlife only, whereas CEQGs used as part of a site investigation or risk assessment must consider not only wildlife, but also soil, invertebrates, plants, soil to groundwater pathways, human health, and other receptors. TRVs are not based on media but on the receptor.

Finally, default FCSAP TRVs are not intended for remedial purposes (e.g., not intended to be used as cleanup levels). Information obtained by generic TRVs can by used to develop site specific TRVs (Module 2 (FCSAP, 2010b)). The TRVs can be transformed to obtain concentrations in some media to use as a cleanup value. However, it must be understood that such a rehabilitation objective will be to protect only the species for which the TRV has been developed. CEQGs or FEQGs (Federal environmental quality guidelines), on the other hand, are intended to protect the most sensitive species.

1 BACKGROUND

The Federal Contaminated Sites Action Plan (FCSAP) is a program with a primary objective of reducing environmental and human health risks from federal contaminated sites and associated federal financial liabilities by assessing and remediating the highest risk sites. FCSAP provides federal departments, agencies, and consolidated Crown corporations responsible for contaminated sites (also referred to as custodians) with the guidance, tools and resources to achieve this objective.

Under FCSAP, ecological risk assessments (ERAs) are commonly used as a site management tool at federal contaminated sites. FCSAP has developed guidance for ERAs supplemental to the existing CCME guidance (1996a, 1997a). FCSAP ERA guidance consists of a comprehensive main ERA guidance document (FCSAP, 2012a) and several specific technical guidance modules (FCSAP 2010a, 2010b, 2012b, 2013, 2019a, 2019a).

This document is a technical guidance module that recommends values to be used as default wildlife TRVs in effects assessments of ERAs. In this document, wildlife refers to birds and mammals. TRVs for other wildlife receptor groups (i.e., reptiles and amphibians) are not commonly available and therefore not considered in this document. However, a growing depth of toxicological information specific to amphibians and reptiles is available (FCSAP, 2019b, Guidance document on Ecological Risk Assessment - Module 6: Ecological Risk Assessment for Amphibians on Federal Contaminated Sites)). This module presents a set of wildlife TRVs for contaminants or groups of contaminants that are commonly a concern on contaminated sites throughout Canada. Providing default wildlife TRVs for ERAs to federal custodians and their consultants is intended to improve national consistency and transparency in the management of federal contaminated sites. Default wildlife TRVs are selected in this module with the intention of providing a conservative level of protection that is consistent with no more than minimal to low level of effects to common species and with the level of protection inherent in the Canadian Council of Ministers of the Environment (CCME) soil quality guidelines (CCME, 2006; Section 7.5.5). These selected default wildlife TRVs are intended for ERAs on federal contaminated sites where the project scope does not permit the development of site-specific TRVs or the application of a comprehensive weight–of-evidence approach. As mentioned in the preface, the default TRVs selected in this module are not intended for remedial purposes. The TRVs can be transformed to obtain concentration in some media to use as a cleanup value. Nevertheless, it must be understood that such a rehabilitation objective will be to protect only the species for which the TRV has been developed. CEQGs or FEQGs (Federal environmental quality guidelines), on the other hand, are intended to protect the most sensitive species.

1.1 Wildlife Toxicity Reference Values in Ecological Risk Assessments

TRVs are selected and/or developed in the effects assessment stage of an ERA and are defined as an exposure concentration or dose for a contaminant of potential concern (COPC) that is not expected to cause an unacceptable level of effect in a receptor of concern (ROC). TRVs are contaminant-specific and receptor-specific, and they can also be tailored for site-specific situations. TRVs can be classified into

three types according to how they are calculated and applied: (i) dose-based TRVs (units of mg chemical/kg body mass/day); (ii) concentration-based TRVs in exposure media (units of mg chemical/kg media or mg/L); or (iii) concentration-based TRVs in tissues of the ROC (units of mg chemical/kg tissue). Module 2 (FCSAP, 2010b) provides more detailed guidance on using these three different types of TRVs in ERAs.

Wildlife TRVs are often dose-based (units of mg chemical/kg body mass/day) when evaluating risks via dietary ingestion of contaminants. Risks to wildlife are often assessed using food chain models that include all oral sources (e.g., food, water, incidental soil/sediment ingestion). Tissue concentration-based TRVs (units of mg chemical/kg tissue) may also be used to assess risk to wildlife, most commonly for contaminants that bioaccumulate in receptor organisms through the diet and/or contact with exposure media. Tissue-concentration-based TRVs are also commonly referred to as critical body residue (CBR), the internal body or tissue concentration that causes a toxicological response in a receptor (McCarty and Mackay, 1993).

In the effects assessment of an ERA, wildlife TRVs would be selected and/or developed for most ROC/COPC combinations. The main exceptions would be:

1. In situations where there are no relevant published toxicity data and where site-specific toxicity testing is not an option.
2. For those ROCs with measurement endpoints relying on direct measures of effects in the field or laboratory (e.g., using small mammal survey of density, biomass, or net migration to assess potential effects on wildlife from exposure to a mixture of COPCs).
3. When no *a priori* acceptable effect levels have been selected. In this case, however, many of the procedures described in Module 2 (FCSAP, 2010b) would still be used to generate a response profile (i.e., only the last step of identifying a single TRV associated with a specific magnitude of response would be skipped; see Section 4 of the main ERA Guidance document – FCSAP, 2012a).

In combination with an exposure estimate for a receptor from the study site (expressed in same units as the TRV), TRVs are often used during the risk characterization phase of an ERA to derive hazard quotients (HQs). The HQ is the ratio between the estimated exposure level and the TRV. An HQ of 1 is generally used as the benchmark in ERA for interpreting whether risk could be unacceptable (i.e., HQ above 1) or acceptable (i.e., HQ below 1). Acceptable or unacceptable risk means that the effects on the targeted population is negligible or significant for the risk assessor. Specifically, if exposure levels to receptors at the study site do not exceed the TRVs, then no unacceptable risks to receptors would be expected. If exposure levels to receptors at the study site do exceed the TRVs, then it is possible, but not certain, that unacceptable effects are occurring. In the latter case, further information is typically required to reduce uncertainty and refine risk estimates. The main FCSAP ERA guidance document (FCSAP, 2012a) provides more complete guidance on using TRVs in an ERA.

TRVs are but one tool that can be used together with site-specific measures of wildlife exposure as one line of evidence within a comprehensive weight-of-evidence approach to ERAs. Recommendation of default TRVs in this module does not imply that hazard quotients are the only option for assessing risk

on contaminated sites. FCSAP (2010b) describes various methods and considerations for dose-response data analysis (depending on data availability for site-specific ROC/COPC combinations) that move beyond screening-level hazard quotients. Recommendations for dose-response data analysis in support of wildlife risk assessment are also detailed in recent scientific literature (Allard *et al.*, 2010; Hill *et al.*, 2014). Recommendation of default TRVs in this Module also does not preclude the use of additional lines of evidence in an ERA. For example, further evaluation and modelling of population-level effects, as well as field-based observations of wildlife presence/absence, density, other attributes, or possible effects, provide ecological context for application of TRVs within a risk assessment. Specifically for contaminants and receptors where the available TRVs have several limitations, other lines of evidence can provide important additional information. The main FCSAP ERA guidance document (FCSAP, 2012a) provides more complete guidance on applying a weight-of-evidence approach to ERAs.

1.2 Scope of Module

This document selects dose-based wildlife TRVs (units of mg chemical/kg body mass/day) that are recommended for use as default values nation-wide by the ERA practitioner, particularly for screening-level assessments and in cases where site-specific TRVs have not yet been developed or selected. Default wildlife TRVs are selected with the intention of providing a conservative level of protection that is consistent with the level of protection inherent in the Canadian Council of Ministers of the Environment (CCME) soil quality guidelines (CCME, 2006). For the purposes of selecting default values, the intended narrative protection goal was considered to be met when there are no more than minimal to low effects to common species, as long as there are no long-term adverse effects on the local populations or ecosystem functions. Again, TRVs that could be demonstrated to be based on an effect level of 25% or less (i.e., effect concentration 25% (EC_{25})/inhibitory concentration 25% (IC_{25}); CCME, 2006, Section 7.5.5) were considered to represent minimal to low effects to common species.

Other criteria, such as effects to individuals or protected species, were not explicitly considered within the scope of this project and remain to be considered on a site-specific basis. Default FCSAP TRVs are not intended to be applied to remedial management decisions (e.g., clean-up levels), which would require further site-specific considerations including, for example, background concentrations, bioavailability of contaminants, and detailed receptor characteristics.

Module 7 presents default generic TRVs for either birds or mammals, not for specific receptors. If there are more specific receptors of concern at a site, it is still an option to develop a new TRV that considers more receptor- and site-specific characteristics. FCSAP ERA Module 2 (FCSAP, 2010b) provides detailed guidance on developing new TRVs.

Published FCSAP guidance describes the recommended derivation methodology for the development of new and site-specific TRVs (FCSAP, 2010b), which is the preferred approach for federal contaminated sites. However, FCSAP recognizes that the development of site-specific TRVs is not always feasible, in which case the default TRVs selected in this document are available for use. Default TRVs for mammals

and birds are provided for a list of 31 contaminants or contaminant groups, including selected metals, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds ([VOC]; benzene, toluene, ethylbenzene, xylenes), petroleum hydrocarbons (PHCs), polychlorinated biphenyls (PCBs), and dioxins and furans (polychlorinated dibenzo-*p*-dioxins [PCDDs] and polychlorinated dibenzofurans [PCDFs]). These contaminants were selected for inclusion in this module because they are commonly encountered on federal contaminated sites. For contaminants not included in this module, existing federal TRV guidance (Module 2; [FCSAP, 2010b]) should be consulted in the selection and development of TRVs on a site-specific basis , and a selection process similar to that used in the development of this module may be considered. Whether choosing a default FCSAP TRV or developing a site-specific value for application in an ERA, the risk assessor ultimately has to make a decision that is supported by defensible rationale.

Each of the recommended default TRVs in this module is assigned a quality rating based on the individual TRV's merits, limitations, and uncertainties. Highlighting these merits, limitations, and uncertainties is intended to assist federal site custodians in making decisions regarding where the development of site-specific TRVs may be warranted. The grade assigned to selected default FCSAP TRVs will help custodians identify where an assessment of risk may be driven by a TRV with substantial limitations and uncertainty and where an assessment of risk is driven by a TRV that is supported by a large dataset and is consistent with FCSAP's recommended TRV derivation methodology (2010b). The assigned grades will also help provide a consistent basis for discussing potential implications of TRVs' uncertainties for the effects assessment and within the overall ERA.

1.3 Wildlife Toxicity Reference Values Considered for this Module

Wildlife TRVs are available from a wide variety of published and unpublished sources and can vary substantially due to differences in underlying toxicological data quality and diversity, protection goals, and/or derivation methodologies. This project has not developed new wildlife TRVs, but rather has evaluated existing values from commonly used sources. Candidate default wildlife TRVs were individually evaluated and assigned a grade based on their overall consistency with FCSAP guidance for TRV derivation (FCSAP, 2010b) and the degree of confidence in their overall suitability as a default for federal contaminated sites.

There were limitations to the criteria used to select default wildlife TRVs for FCSAP, including:

i. Protection of human health from consumption of mammals or birds was not taken into consideration. Please refer to Health Canada for recommendations regarding protection of human health from wildlife consumption.
ii. Selection of default TRVs generally did not consider the cumulative impact of chemical mixtures on wildlife receptors (with the exception of those TRVs for contaminant groups sharing a common mode of toxic action). Wildlife may be exposed to a broad suite of contaminants (e.g., multiple metals) at federal contaminated sites. At this time, TRVs that explicitly account for combined effects of contaminants operating through varied modes of toxic action are generally not available. TRVs for contaminant mixtures are limited to a few

contaminant groups that are believed to operate through a shared mode of toxic action (e.g., polycyclic aromatic hydrocarbons share a non-polar narcosis mode of toxic action).

iii. TRV selection focused on oral exposure pathways (e.g., exposure through diet), which is typically considered the dominant exposure pathway in wildlife risk assessments. However, there may be merit in some cases to more explicitly consider other pathways, such as inhalation or dermal exposure pathways (CCME, 2006).

iv. TRV selection focused on dose-based TRVs (units of mg chemical/kg body mass/day). There may be merit in some cases to include other types of TRVs for assessing risks to wildlife, such as TRVs based on concentrations in the diet or exposure media (units of mg chemical/kg media or mg chemical/L). Tissue-concentration-based TRVs (units of mg chemical/kg tissue) are another type of TRVs commonly used for bioaccumulative contaminants (FCSAP, 2010a). For example, the British Columbia Ministry of Environment (BCMOE) developed a tissue guideline for selenium in bird eggs, for protection of wildlife (BCMOE, 2014).

v. Module 7 focused on TRVs derived from toxicological endpoints of survival, growth, and reproduction. However, other endpoints may be relevant for consideration in site-specific ERAs for mammals and birds, including protected species. For example, some of the contaminants considered in this report, such as PAHs, have also been associated with cancer in wildlife (McAloose and Newton, 2009). Cancer has not been directly considered as an endpoint in this evaluation.

2 GUIDANCE

This section presents the recommended default values for FCSAP, as well as the grade (A, B, or C) assigned to each receptor- and contaminant-specific default FCSAP TRV. A default FCSAP TRV's grade is based on an evaluation of its overall consistency with FCSAP guidance for TRV derivation and the degree of confidence in its suitability as a default for federal contaminated sites. Detailed information and supporting rationale behind the selection of each default FCSAP TRV is provided in **Appendix A**. The user of this module is strongly urged to review **Appendix B**, which describes the methods and criteria that were used to select default FCSAP TRVs. These methods were based on FCSAP (2010b) guidance for TRV development. Evaluation methods included a set of 10 characteristics that were evaluated for each candidate TRV: (i) number of studies used in TRV derivation; (ii) lowest-observed-adverse-effects level (LOAEL), no-observed-adverse-effects level (NOAEL) or dose-response derivation methods; (iii) bound or unbound toxicity data (for LOAEL/NOAEL-based TRVs); (iv) use of allometric scaling; (v) use of uncertainty factors; (vi) species tested in underlying toxicological tests; (vii) endpoints; (viii) relevance of experimental exposure conditions and pathways, ix) level of protection; and (x) any other major concerns identified for a candidate TRV. **Appendix B** can be consulted for more details on how each of these characteristics were evaluated. The sources that were reviewed to identify candidate default TRVs for evaluation are described in **Appendix C**. Further guidance on how TRVs are used in an ERA is provided in the main FCSAP ERA guidance document (FCSAP, 2012a). All TRVs presented in this module were current at the time of developing Module 7. The user is responsible for ensuring that TRVs are current at the time of use and that TRVs used in risk assessments are appropriate for the specific site.

2.1 How to Interpret Grades Assigned to Selected Toxicity Reference Values

The TRVs evaluated in this project have a wide range of merits and limitations across the different receptor groups and contaminants, ultimately resulting in varying degrees of confidence across the selected TRVs in terms of how well they align with FCSAP guidance on TRV derivation. The application of a grading system to the selected default FCSAP TRVs will help custodians, consultants, and government evaluators explicitly acknowledge sources of uncertainty and limitations underlying selected TRVs used for effects assessments in ERAs. The analysis presented in this report will also help facilitate an understanding and consideration, in a consistent manner across federal sites, of the potential implications of selected TRVs' limitations for risk assessments at federal contaminated sites. The level of confidence associated with a given default TRV was denoted by one of three grades (A, B, or C). In some cases, no default FCSAP TRV was selected. Either there were no TRVs available to evaluate at the time of writing (i.e., N/A - none available), or the TRVs that were available and evaluated were considered insufficient and inappropriate for use as a default FCSAP value (i.e., N/S - none suitable). Each of the five possible grades (A, B, C, N/A, and N/S) are described in detail below.

GRADE A

The TRVs in this category are recommended as default TRVs for FCSAP because they are generally consistent with FCSAP TRV guidance, and there is a high degree of confidence in their overall suitability as a default for federal contaminated sites. For TRVs designated as Grade A, sufficient information was available about the underlying toxicology data, the derivation methodology was generally consistent with FCSAP recommended guidance (FCSAP, 2010b), and they are likely to provide a conservative level of protection associated with no more than a low to minimum level of effects to common species (i.e., EC_{25}/IC_{25}; CCME, 2006, Section 7.5.5).

These selected default TRVs are still not without limitations. For example, in some cases there is lack of quantification of the effect size associated with the selected TRV. To improve upon these limitations, future TRV derivation should apply methodology outlined in FCSAP (2010b), which is more in line with current scientific recommendations (e.g., Allard *et al.*, 2010). For example, compilation and analysis of dose-response data from a broad set of relevant toxicity studies could lead to TRVs with an associated quantitative level of protection. However, those steps are low priority at this point for receptors and contaminants with Grade A TRVs, as they are unlikely to change the outcome of the evaluation used in this module to select default FCSAP TRVs.

Site-specific TRVs for a particular site that are developed following FCSAP guidance (FCSAP, 2010b) may still be used in lieu of these default TRVs. Developing site-specific TRVs can be time-consuming, but is typically advantageous because they can incorporate site-specific conditions and objectives and thus result in a more reliable assessment of risk for a particular site.

GRADE B

The TRVs in this category are recommended as default TRVs for FCSAP, but because they have some inconsistencies with FCSAP TRV guidance, there is a moderate degree of confidence in their overall suitability as a default for federal contaminated sites. Examples of some limitations of Grade B TRVs include limited underlying toxicological datasets or a lack of quantified effect size (e.g., TRV based on a NOAEL).

If risk assessment at a site is driven by a Grade B TRV:

- Consult the receptor- and contaminant- specific evaluation in **Appendix A** to review limitations and rationale for the moderate grade assigned to the default FCSAP TRV;
- Consider the implications of TRV's limitations on a site-specific basis and possible steps to improve upon or remedy these limitations (including potentially deriving site-specific TRVs); and/or
- Investigate other lines of evidence to inform the risk assessment.

GRADE C

The TRVs in this category are recommended as default TRVs for FCSAP, but because they have substantial inconsistencies with FCSAP TRV guidance, there is a low degree of confidence in their overall suitability as a default for federal contaminated sites. An example of a limitation of a Grade C TRV is derivation from a single toxicological study. Although Grade C TRVs satisfy very few of the criteria used to select default values, in many cases they represent the only available TRVs for a contaminant and receptor, and the limitations that were identified did not preclude their use as default values for FCSAP. Therefore, TRVs in this category may be applied as defaults at federal contaminated sites because of the lack of a more appropriate substitute, but it is important to recognize their substantial limitations and the possible implications of the uncertainty associated with Grade C TRVs for an ERA.

If risk assessment at a site is driven by a Grade C TRV:

- Consult the receptor- and contaminant- specific evaluation in **Appendix A** to review specific limitations and rationale for the low grade assigned to the default FCSAP TRV;
- Consider implications of the TRV's limitations on a site-specific basis and identify possible steps to improve upon or remedy these limitations;
- Consider the development of site-specific TRVs, and/or application of TRV derivation methodology described in Module 2 (FCSAP, 2010b) using existing available toxicological data;
- Consider a review of the primary literature for additional toxicity data to include in the development of site-specific TRVs that applies current recommended methodology (FCSAP, 2010b);
- Consider applying other relevant approaches for addressing limited toxicity data in an effects assessment (e.g., Hill *et al.*, 2014); and/or
- Investigate other lines of evidence to incorporate into the risk assessment.

None Suitable (N/S)

Some contaminants and receptors had candidate TRVs that were evaluated but considered to be inappropriate or insufficient as a default value for federal contaminated sites on the basis of the selection criteria applied in this module. The limitations and uncertainties associated with TRVs available for these contaminants and receptors were considered substantial enough to prevent selection as a default value for FCSAP. In particular, TRVs suspected as being associated with greater than minimal to low level of effects (e.g., TRVs derived from an LC_{50} or from a LOAEL with an unquantified effect size) were not selected as a default value for FCSAP. Other examples include: TRVs based on only one single-dose exposure study; TRVs based on data for endpoints of uncertain biological relevance (e.g., immunosuppression); large, un-resolvable discrepancies across candidate TRVs; limited toxicity data; or TRVs based on a single unbound NOAEL.

If risk at a site is suspected to be driven by a contaminant for which there was no suitable default TRV:

- TRVs that were evaluated but not selected (see **Appendix A** for not-selected TRVs) will not be accepted for use as a default on FCSAP sites;
- Consult the receptor- and contaminant- specific evaluation in **Appendix A** to review specific limitations and rationale for not selecting any of the available candidate values as a default;

- Consider the implications of available TRVs' limitations on a site-specific basis and identify possible steps to improve upon or remedy these limitations;
- Evaluate the available TRVs against site-specific considerations to determine their suitability for site-specific circumstances;
- Consider the development of site-specific TRVs and/or application of TRV derivation methodology described in Module 2 (FCSAP, 2010b) using existing available toxicological data;
- Consider a review of the primary literature for additional toxicity data to include in the development of site-specific TRVs that applies current recommended methodology (FCSAP, 2010b);
- Consider applying other relevant approaches for addressing limited toxicity data in an effects assessment (e.g., Hill *et al.*, 2014); and/or
- Investigate other lines of evidence to incorporate into the risk assessment.

None Available (N/A)

There were no TRVs or toxicological data available to evaluate from any of the consulted TRV sources. If risk at a site is suspected to be driven by a contaminant for which there were no values available:

- Potentially consider a more thorough review of the primary literature for additional toxicity data to which FCSAP (2010b) methodology and/or other relevant approaches for addressing limited toxicity data in an effects assessment (e.g., Hill *et al.*, 2014) can be applied; and/or
- Investigate other lines of evidence and/or rationale to evaluate the risk of adverse effects from these contaminants.

2.2 Default FCSAP Toxicity Reference Values

Table 1 below summarizes the recommended default FCSAP TRVs and their assigned grade. For some receptors and contaminants, no TRV could be recommended as a default for FCSAP at time of writing because either (i) no TRVs were available for evaluation (i.e., N/A, none available), or (ii) none of the available candidate TRVs were considered suitable as a default value for FCSAP (i.e., N/S, none suitable). It is strongly recommended to read **Appendix A** to gain an understanding of each TRV's merits and limitations and their possible implications in context of individual sites before using any of the recommended default FCSAP TRVs in site-specific ecological risk assessments.

Table 1: Dose-based wildlife toxicity reference values (TRVs) recommended by the Federal Contaminated Sites Action Plan (FCSAP) as default values for use in ecological risk assessments (consult Appendix A for important details to consider when applying each TRV) [1].

Chemical	Mammals			Birds		
	Grade[2]	TRV (mg/kg bm/day)	Source[3]	Grade[2]	TRV (mg/kg bm/day)	Source[3]
Metals and Inorganics						
Arsenic (inorganic)	A	1.04	USEPA 2005a	A	4.4	CEAEQ 2012
Barium	C	51.8	USEPA 2005b	B	51.3	CEAEQ 2012
Cadmium	A	0.77	USEPA 2005c	B	2.1	CEAEQ 2012
Chromium (hexavalent)	B	9.24	USEPA 2008	C	16	Condor *et al.* 2009
Chromium (total)	C	2.4	USEPA 2008	C	2.66	USEPA 2008
Copper	A	5.6	USEPA 2007a	A	4.5	CEAEQ 2012
Free Cyanide ($HCN+CN^-$)	N/S			N/S		
Lead	B	4.7	USEPA 2005d	B	1.63	USEPA 2005d
Mercury (inorganic)	B	5.8	CEAEQ 2012	B	0.8	CEAEQ 2012
Nickel	B	1.7	USEPA 2007b	B	6.71	USEPA 2007b
Selenium	B	0.143	USEPA 2007c	B	0.29	USEPA 2007c
Thallium	B	0.015	Williams *et al.* 2015	N/S		
Uranium	B	6.13	Sample *et al.* 1996	N/S		
Vanadium	B	4.16	USEPA 2005e	B	0.344	USEPA 2005e
Zinc	B	75.4	USEPA 2007e	B	66.1	USEPA 2007e
Low Molecular Weight Polycyclic Aromatic Hydrocarbons (LMW PAHs)						
Anthracene	N/S			N/A		
Fluorene	N/S			N/A		
Naphthalene	B	14.3	LANL 2014	C	7.7	Klasing 2007
Phenanthrene	N/S			N/A		
LMW PAHs	B	65.6	USEPA 2007d	C	7.7	Parametrix *et al.* 2010
High Molecular Weight Polycyclic Aromatic Hydrocarbons (HMW PAHs)						
Benz(a)anthracene	N/S			C	0.107	LANL 2014
Benzo(a)pyrene	C	3.6	CEAEQ 2012	C	0.001	USEPA 1999
Pyrene	N/S			C	20.5	LANL 2014
HMW PAHs	B	0.615	USEPA 2007d	N/S		
Volatile Organic Compounds (VOCs)						
Benzene	B	2.62	Sanexen 2002	N/A		
Ethylbenzene	C	0.7	Sanexen 2002	N/A		
Toluene	C	26	Sample *et al.* 1996	N/A		
Xylenes	N/S			C	107	LANL 2014

Chemical	Mammals			Birds		
	Grade[2]	TRV (mg/kg bm/day)	Source[3]	Grade[2]	TRV (mg/kg bm/day)	Source[3]
Petroleum Hydrocarbons (PHCs)						
Total PHCs;	C	210	CCME 2008	C	125	Szaro 1977
CCME CWS Fractions	C	F1: 48.72; F2: 44.73; F3: 72.45; F4: 38.22	AEP (2016) and CCME (2008)	N/A		
Polychlorinated Biphenyls (PCBs) and Polychlorinated Dibenzo-*p*-dioxins (PCDDs) / Polychlorinated Dibenzofurans (PCDFs)						
Total PCB TEQ	C	0.19 ng TEQ / kg bm/day	CCME 2001a	C	2.3 ng TEQ / kg bm/day	CCME 2001a
Total PCDD/F TEQ	C	0.17 ng TEQ / kg bm/day	CCME 2001b	C	4.47 ng TEQ / kg bm/day	CCME 2001b

Abbreviations for Table 1:

AEP = Alberta Environment and Parks; **CCME** = Canadian Council of Ministers of the Environment; **CEAEQ** = Centre d'expertise en analyse environnementale du Québec; **CWS** = Canada-wide standard; **HMW** = high molecular weight; **LANL** = Los Alamos National Laboratory; **LMW** = low molecular weight; **N/A** = none available; **N/S** = none suitable; **PAHs** = polycyclic aromatic hydrocarbons; **PCBs** = polychlorinated biphenyls; **PCDD** = polychlorinated dibenzo-*p*-dioxins; **PCDF** = polychlorinated dibenzofurans; **PHCs** = petroleum hydrocarbons; **TEQ** = toxic equivalency factors; **TRV** = toxicity reference value; **USEPA** = United States Environmental Protection Agency; and **VOC** = volatile organic compounds.

Footnotes for Table 1:

1. See **Appendix A** for a detailed description of the merits and limitations associated with each contaminant/receptor pair. **Appendix A** also contains a full list of all candidate TRVs for each contaminant and receptor that were evaluated as potential default FCSAP TRVs.

2. Each contaminant/receptor pair was assigned one of the following five grades on the basis of overall consistency with FCSAP guidance for TRV derivation and degree of confidence in overall suitability as a default for federal contaminated sites (see **Section 2.1** of this report for further implications of each grade):

A = Recommended as a default TRV for FCSAP, generally consistent with FCSAP TRV guidance and high degree of confidence in its overall suitability as a default for federal contaminated sites.

B = Recommended as a default TRV for FCSAP, but with some inconsistencies with FCSAP TRV guidance and moderate degree of confidence in its overall suitability as a default for federal contaminated sites.

C = Recommended as a default TRV for FCSAP, but with substantial inconsistencies with FCSAP TRV guidance and low degree of confidence in its overall suitability as a default for federal contaminated sites.

N/S = None Suitable. No TRV was recommended as a default for FCSAP because none of the available TRVs were considered suitable to meet FCSAP criteria.

N/A = None Available. No TRV was recommended for FCSAP because none were available for evaluation.

3. Source of TRV lists the main citation where TRV was first published. Selected TRVs may have also been selected or cited by other sources not listed in this table (e.g., Allaway and Stodola, 2011; Dillon, 2013).

2.3 Moving Towards Improved Wildlife Toxicity Reference Values in Ecological Risk Assessments

Various limitations are associated with existing TRVs currently available for application in ERAs (Mayfield and Fairbrother, 2012; Mayfield *et al.*, 2013), including limitations associated with the TRVs that have been selected in this module as default values for FCSAP. Therefore, there remains room to improve future wildlife TRVs (both site-specific and any generic or future default FCSAP TRVs) by applying recommended methodology for TRV derivation, as described in FCSAP (2010b). Some of the general key points to be considered for future TRV evaluation and development include:

- Compilation of dose-response data from toxicological studies;
- Quantification of the effect size associated with toxicological data;
- Quantification of the uncertainty associated with toxicological response data (e.g., confidence interval around an EC_{20} calculated from dose-response data);
- Integration of information across multiple studies, rather than reliance on single individual toxicological studies; and,
- Consideration of a review of TRVs derived for protection of human health, which are often based on rodent toxicological data and therefore potentially relevant for deriving new mammalian wildlife TRVs.

Potential products arising from future TRV evaluation and development processes could include the compilation of a comprehensive database of dose-response data (as recommended in Allard *et al.*, 2010). This would greatly aid the broader community of ERA practitioners and could help reduce duplicative efforts by multiple agencies using similar data for ultimately the same purpose of evaluating risks to wildlife from exposure to contaminants.

When new TRVs are derived in the future (either future default values for FCSAP or site-specific values), assignment of priority should take into consideration the grades of existing default TRVs and prioritize receptor/contaminant pairs with either no selected default value or lower graded TRVs.

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APPENDIX A: SUPPORTING SCIENTIFIC RATIONALE FOR INDIVIDUAL TOXICITY REFERENCE VALUE EVALUATIONS

A.1. Introduction

Appendix A provides a detailed summary of the characteristics, merits, and limitations of selected default TRVs, as well as supporting rationale behind the selection of each default TRV for each contaminant of potential concern and wildlife receptor group (mammals and birds) within the scope of this module. It is strongly recommended that the user of this module refer to **Appendix B** for a detailed description of the methods and criteria used to evaluate the merits, limitations, and uncertainties of candidate TRVs.

Users may refer to the original sources of TRVs for full details on their derivation, including any additional parameters used to calculate these TRVs (e.g., ingestion rates and body mass used to calculate a TRV in units of mg/kg body mass/day from a diet concentration).

Each summary sheet will include the following sections:

Chemical Name
Receptor: Mammals or Birds

Selected TRV = ### mg/kg body mass/day
Source: from where the TRV was obtained
Grade assigned to the selected default TRV = one of five options:

Grade A = Recommended as a default TRV for FCSAP, generally consistent with FCSAP TRV guidance, and high degree of confidence in its overall suitability as a default for federal contaminated sites.

Grade B = Recommended as a default TRV for FCSAP, but with some inconsistencies with FCSAP TRV guidance and moderate degree of confidence in its overall suitability as a default for federal contaminated sites.

Grade C = Recommended as a default TRV for FCSAP, but with substantial inconsistencies with FCSAP TRV guidance and low degree of confidence in its overall suitability as a default for federal contaminated sites.

None Suitable (N/S) = No TRV was recommended as a default for FCSAP because none of the available TRVs were considered suitable to meet FCSAP criteria.

None Available (N/A) = No TRV was recommended for FCSAP because none were available for evaluation.

Basis for the selected TRV

A couple of sentences summarizing the selected TRV's evaluation against the selection criteria laid out in **Appendix B**, including:

- Source of TRV (e.g., USEPA, Sample *et al.*, 1996) and references of underlying toxicological data
- Derivation methods: LOAEL/NOAEL (bound or unbound) or dose-response
- Biological endpoints (e.g., survival, growth, or reproduction)
- Number of toxicological studies used to derive the TRV

- Any use of allometric scaling
- Any use of uncertainty factors
- Receptor of concern for which the TRV was developed

Merits of the selected TRV

Highlight the merits of the selected TRV. What qualities of the selected TRV are consistent with FCSAP's preferred methodology and selection criteria as described in **Appendix B**? For example, does the selected TRV consider a large number of studies; is it based on a quantified effect level (e.g., an EC_{20}) and/or a dose-response curve; does it consider toxicity data representing a variety of species?

Limitations of the recommended default TRV

Are there any concerns with using this TRV as a FCSAP default recommended value? Which evaluation criteria (in **Appendix B**) does the selected TRV not meet? Are there data gaps that are not considered in the development of the selected TRV (e.g., limited species)? Is the effect size or level of protection behind the TRV not quantified?

Evaluation of candidate TRVs

This section presents a list of all the TRVs that were evaluated as candidates to potentially be selected as the recommended default TRVs for FCSAP. This section also discusses the selected default TRVs in context against the other evaluated candidate TRVs. For example:

- How did the selected default TRVs compare, both numerically and qualitatively, to other candidate TRVs that were also evaluated for this receptor and contaminant of potential concern?
- What were the consistencies or discrepancies between the selected default TRVs and other available candidate TRVs or data?
- Did the candidate TRVs available for evaluation span a wide range of values?
- Were there many different candidate TRVs based on different studies and methodology, or were there only a few candidate TRVs available based on the same underlying toxicological study?
- In some cases, a reference provided multiple candidate TRVs based on different effect levels or narrative intentions. For example, CEAEQ (2012) often had two candidate TRVs evaluated, representing a reported EC_{20} and EC_{40}. In these cases, all TRVs presented in the reference were considered in the selection process.
- In some cases, a reference presented multiple TRVs for different receptor categories. For example, for some contaminants of potential concern, Allaway and Stodola (2011) and Dillon (2013) recommended one TRV for raptors and another TRV for non-raptor avian species. This module did not distinguish between receptor categories more specific than either mammals or birds. Therefore, all TRVs presented in the original source were considered in the selection process as a candidate TRV for generic birds or generic mammals.

Suggestions for improved future TRVs

On the basis of the assigned grade of the selected TRV (see above) and its overall limitations and uncertainties, some general suggestions for developing TRVs (either future default FCSAP TRVs or site-specific TRVs) are made for future consideration.

A.2. Selected Mammalian Toxicity Reference Values: Supporting Scientific Rationale

Arsenic [Metalloid]

Receptor: Mammals

Selected TRV = 1.04 mg/kg bm/day
Source: USEPA, 2005a
Grade: A

Basis for the selected TRV

This TRV is from an USEPA (2005a) dataset of 55 toxicological studies and is the highest bound NOAEL below the lowest bound LOAEL for relevant biological endpoints. This highest bound NOAEL corresponds to a toxicity study by Neiger and Osweiler (1989) exposing beagle dogs to sodium arsenite in food over an 8-week study period at dose levels of 0, 1, 2, and 4 mg sodium arsenite/kg bm/day. The 2 and 4 mg sodium arsenite/kg bm/day dose levels corresponded to the NOAEL and LOAEL for growth. Overall, this TRV from USEPA (2005a) incorporated a range of toxicity data for variety of species including rat, mouse, rabbit, guinea pig, dog and goat, and for a variety of endpoints (specifically reproduction, growth, survival).

Merits of the selected TRV

The TRV was derived using multiple studies (n=55), multiple mammalian species (6), and multiple endpoints (survival, growth, and reproduction) and therefore reflects a broader range of exposure conditions and receptors compared to a TRV derived from a single study. No uncertainty factors were applied.

Limitations of the recommended default TRV

Limitations of the selected TRV are (1) that it was derived using NOAEL/LOAEL methods and (2) that more than two-thirds of the NOAELs or LOAELs used in the derivation of this TRV were unbound values. It is unclear whether allometric scaling or other conversion factors were applied to the selected TRV, because of the discrepancy between the dose levels reported in the original study (Neiger and Osweiler, 1989; 2 mg/kg bm/day) and in USEPA (1.04 mg/kg bm/day). Additionally, the test duration was only 8 weeks, which may not be representative of chronic environmental exposure conditions, although overall test durations in the USEPA dataset ranged between 5 days and 2 years.

Evaluation of candidate TRVs

Table A.1. Candidate mammalian toxicity reference values (TRVs) for arsenic

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.32	USEPA Region 9 BTAG, 2009
1.04	**USEPA 2005a; Dillon, 2013**
1.26	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
2.9	Rae, 2013
2.9	CEAEQ, 2012
4.7	USEPA Region 9 BTAG, 2009
5.7	Rae, 2013
8	CCME, 1997b

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Eight TRVs, ranging from 0.32 to 8 mg/kg bm/day, were evaluated. Three of these TRVs were derived from reproduction, growth, and survival endpoints in the toxicity dataset in USEPA (2005a) and are equal to the highest bound NOAEL below the lowest bound LOAEL (1.04 mg/kg bm/day; USEPA, 2005a), the geometric mean of reproductive, growth, and survival NOAELs (2.9 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (5.7 mg/kg bm/day). All three of these TRVs share similar merits, such as being based on a variety of studies, species, and endpoints. However, none of the three provide a quantitative measure of the level of effect that they represent. There is therefore no clear method at this time for selecting the TRV that provides a level of protection most consistent with a minimal to low level of effects. The most conservative TRV (1.04 mg/kg bm/day; USEPA, 2005a) was thus selected as the FCSAP default TRV.

CEAEQ (2012) applied dose-response methodology to calculate EC_{20} from individual toxicity studies and selected the lowest EC_{20} values across four studies as the basis for their TRV (2.9 mg/kg bm/day). These four studies included data for dog, rat, and mouse exposed to arsenic through diet for up to 2 years. This TRV was associated with a 20% effect level, which provides a level of protection that is consistent with a minimal to low level of effects. However, uncertainty factors were applied (mortality endpoints were divided by 5, sub-lethal endpoints were divided by 2.5, acute exposure durations were divided by 2). The use of uncertainty factors that are not supported by scientific rationale is not consistent with current recommended methodology (FCSAP, 2010b) and is therefore considered a limitation of this TRV from CEAEQ (2012).

The remaining four TRVs were all derived from single toxicity studies (0.32, 1.26, 4.7, and 8 mg/kg bm/day). The highest value (8 mg/kg bm/day; CCME, 1997b) is an LD_{50} and therefore too severe to be selected as a default value for FCSAP. All of these TRVs that were based on single studies do not allow an evaluation of how the TRV compares within the context of a broader range of information about a variety of species, endpoints, or exposure conditions, as is relevant for FCSAP default values.

Suggestions for improved future TRVs

Dose-response data from studies in the USEPA (2005a) dataset could be further investigated to derive improved TRVs with a more quantified level of protection. This step, although likely an intense effort, would be an improvement on the USEPA TRV, which is based on a NOAEL and therefore considered potentially overly conservative. This step would likely lead to derivation of a TRV that is more aligned

with FCSAP TRV guidance (FCSAP, 2010b) and that can be more quantitatively demonstrated to provide an appropriate level of protection. However, the selected TRV is considered likely to provide a sufficient level of protection and to be associated with no more than minimal to low effects to common species. The comprehensive methodology used to arrive at this TRV and the fact that it is derived on the basis of the results of multiple toxicity studies make it the best choice for a default FCSAP TRV at this time.

Barium [Metal]

Receptor: Mammals

Selected TRV = 51.8 mg/kg bm/day
Source: USEPA, 2005b
Grade: C

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 27 data points from 10 toxicological studies and is the geometric mean of eight NOAELs for growth or reproduction (four of which are bound). All studies considered were conducted on either mice or rats, using exposure routes of gavage, food or drinking water. Test durations ranged from acute to chronic (10 to 520 days).

Merits of the selected TRV

Derivation of the selected TRV considered 10 different toxicological studies and a number of relevant biological endpoints (both growth and reproduction) to calculate a geometric mean. Therefore, this TRV integrates a broad range of toxicological data and better reflects the wide variety of environmental exposure conditions and receptors than does a TRV that has been derived from a single toxicological study. Other merits of this TRV are that no allometric scaling or uncertainty factors were applied in deriving the TRV.

Limitations of the recommended default TRV

The main limitation of this TRV is an overall lack of available mammalian toxicity data for barium. Of the studies that are available, half are unbound NOAELs that do not provide a complete picture of the dose-response relationship. Additionally, the USEPA study database covers only two species, namely rat and mouse, so it is unclear that the TRV is applicable to all mammalian species. Some of the underlying toxicity data used gavage methodology to expose test animals, which is not considered a particularly relevant exposure pathway. The study uses a NOAEL-based approach calculating a geometric mean from 8 NOAELs, so there is a possibility that the TRV is overly conservative as a default for FCSAP. However, there is no quantitative information to evaluate the level of protection provided by this TRV.

Evaluation of candidate TRVs

Table A.2. Candidate mammalian toxicity reference values (TRVs) for barium

Candidate TRV (mg/kg bm/day)	**Source (See Reference Section 3)[1]**
5.06	Sample *et al.*, 1996
18.4	CEAEQ, 2012
19.8	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
51.8	**USEPA, 2005b; Allaway and Stodola, 2011; Dillon, 2013**
64	Rae, 2013
120	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

The range of the TRVs is from 5.06 mg/kg bm/day to 120 mg/kg bm/day. The three lowest TRVs were based on only one or two studies each and therefore do not provide any information regarding how these TRVs fit within the context of a broader range of information about a variety of species, endpoints, or exposure conditions, as is relevant for FCSAP goals. The lowest available candidate TRV (5.06 mg/kg bm/day; Sample *et al*., 1996) was based on an unbound NOAEL for growth in rats, suggesting that this TRV may be overly conservative. CEAEQ (2012) also derived a TRV of 18.4 mg/kg bm/day from the same toxicological study behind the 5.06 mg/kg bm/day TRV from Sample *et al*. (1996). CEAEQ (2012) applied a dose-response methodology to calculate an EC_{20} for a hypertension endpoint in rats exposed to barium in drinking water for 16 months. CEAEQ (2012) also considered an EC_{20} for mortality from one other study, but selected the 18.4 mg/kg bm/day because it was lower. The CEAEQ (2012) TRV was not selected for FCSAP because it was based on a hypertension endpoint, which has uncertain relevance as a default value. The second TRV from Sample *et al.* (1996; 19.8 mg/kg bm/day) was based on a LOAEL for survival in female rats exposed to barium for 10 days via oral gavage. This TRV was not selected as a default value for FCSAP because the underlying LOAEL (198 mg/kg bm/day) was associated with 30% mortality, which is too severe an effect level for a default TRV for FCSAP, and there is no supporting scientific rationale that the uncertainty factor (LOAEL divided by 10) would result in an acceptable effect level.

The remaining three TRVs are based on the USEPA dataset and represent the geometric mean of reproduction and growth NOAELs (51.8 mg/kg bm/day; USEPA, 2005b), the geometric mean of reproduction, growth, and survival NOAELs (64 mg/kg bm/day), or the geometric mean of reproduction, growth, and survival LOAELs (120 mg/kg bm/day). All three of these TRVs are based on multiple studies. However, none of the three provide a quantitative measure of the level of effect that they represent. The geometric mean of LOAELs (120 mg/kg bm/day; Rae, 2013) is potentially biased low by the lowest of the eight LOAELs in that dataset (0.74 mg/kg bm/day; growth endpoint), which is much lower than the remaining seven LOAELs in that dataset (between 121 and 436 mg/kg bm/day; geometric mean of those seven LOAELs = 246 mg/kg bm/day). Without a more quantitative evaluation of the level of effect associated with the toxicological data underlying these three candidate TRVs, there is no clear method for selecting the TRV that provides a level of protection most consistent with a minimal to low level of effects. Therefore, the most conservative of the three TRVs based on the USEPA dataset (51.8 mg/kg bm/day; USEPA, 2005b) was selected as a default value.

Suggestions for improved future TRVs

Overall, there is somewhat limited mammalian toxicological data for barium. Furthermore, the selected NOAEL-based TRV had few available LOAEL data that were below the selected TRVs, which leads to a limited understanding of the dose-response relationship and indicates uncertainty with the level of protection provided by the selected default TRV. Therefore, extraction of dose-response data from underlying toxicological studies may facilitate development of an improved TRV. Additionally, updated literature searches for additional toxicology data may help supplement the currently limited set of available data. Derivation of new TRVs should apply FCSAP-recommended methodology for TRV development.

Cadmium [Metal]

Receptor: Mammals

Selected TRV = 0.77 mg/kg bm/day
Source: USEPA, 2005c
Grade: A

Basis for the selected TRV

This TRV is from an USEPA dataset of 145 toxicological studies (2005c) and is the highest bound NOAEL below the lowest bound LOAEL for the survival, growth, and reproduction endpoints identified in the USEPA dataset. The species represented by this dataset include rat, mouse, sheep, pig, cattle, rabbit, bank vole and shrew. The selected TRV is therefore considered to be representative of a wide variety of mammals. However, the TRV may potentially be overly conservative because it is derived using NOAEL-based methodology.

Merits of the selected TRV

Although the specific dose level of the selected TRV is from a single toxicological study (Yuhas *et al.*, 1979), the USEPA TRV derivation methodology considered a large dataset of 145 toxicological studies that included multiple species, exposure pathways, and endpoints. Yuhas *et al.* (1979) exposed rats to different dose levels (0, 1, 10, and 100 mg/L) of cadmium acetate in their drinking water. The biological endpoint used to study effects was growth, with the selected TRV being a NOAEL (10 mg/L) that is bound by a LOAEL (100 mg/L). No allometric scaling or uncertainty factors were applied.

Limitations of the recommended default TRV

The main limitation with this TRV is that it is a bound NOAEL near the lower end of a distribution of a large number of NOAELs from various studies. This TRV is below 76 out of 81 LOAELs in the USEPA dataset from which it was derived and is therefore likely to be conservative for FCSAP purposes. The LOAEL of 0.909 mg/kg bm/day that corresponds to the NOAEL behind this selected TRV is also lower than the other candidate mammalian TRVs for cadmium. Another potential limitation is that the exposure duration in the study is acute (2 weeks), although more chronic studies are also present in the USEPA dataset used to derive the selected TRV.

Evaluation of candidate TRVs

Table A.3. Candidate mammalian toxicity reference values (TRVs) for cadmium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.77	**USEPA, 2005c; Dillon, 2013**
2.3	Rae, 2013
2.64	USEPA Region 9 BTAG, 2009; Allaway and Stodola, 2011
2.6	CEAEQ, 2012
2.9	CEAEQ, 2012
2.9	OMOE, 2011; Allaway and Stodola, 2011
4.56	CCME, 1999a; OMOE, 2011; Allaway and Stodola, 2011
7.1	Rae, 2013
10	Sample *et al.*, 1996

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Nine mammalian TRVs for cadmium, ranging from 0.77 to 10 mg/kg bm/day, were evaluated. Of these nine TRVs, three were not selected because they are not sufficiently protective and are likely associated with more than minimal to low effects to common species: 2.64 mg/kg bm/day (Allaway and Stodola, 2011; USEPA Region 9 BTAG, 2009), 2.9 mg/kg bm/day (CEAEQ, 2012), and 10 mg/kg bm/day (Sample *et al.*, 1996). The 2.64 mg/kg bm/day TRV (USEPA Region 9 BTAG, 2009) was presented as a "TRV-High", which was narratively described as a dose that "would be expected to produce an adverse effect to an individual or population of organisms," which was not considered an appropriate intention for a default FCSAP TRV. The 2.9 mg/kg bm/day TRV (CEAEQ, 2012) represents a 40% effect level. The TRV from Sample *et al.* (1996; 10 mg/kg bm/day) was derived from a LOAEL from one study and was associated with over 20% effect level in reproductive endpoints in rats (28% reduced fetal implantations; 50% reduced fetal survivorship; 400% increased fetal reabsorption).

Three TRVs were considered less appropriate as a FCSAP default TRV than the USEPA-based candidate TRVs because they were based on more limited datasets. The 2.9 mg/kg bm/day TRV from OMOE (2011) was based on a LOAEL for growth from a single study. The effect level associated with this LOAEL could not be determined and, combined with additional uncertainties in this TRV's derivation (uncertain use of allometric scaling and uncertainties), was thus considered not sufficiently characterized to be a default FCSAP TRV. The CCME (1999a) TRV of 4.56 mg/kg bm/day was based on NOAEL. However, even though the associated treatment level was not statistically different from control, it still had a 21% reduced body mass growth relative to control, and the uncertainty around the effect level associated with this TRV was therefore considered too high to select it as a default TRV for FCSAP. The second CEAEQ (2012) TRV of 2.6 mg/kg bm/day represents an EC_{20}, which was extrapolated from an LC_{50} from one study. On the basis of CEAEQ (2012) methods and objectives, CEAEQ (2012) had selected that one study out of a set of seven as the most appropriate. Although an EC_{20} was considered appropriate, the availability of candidate TRVs based on a broader dataset precluded selection of this TRV as a default for FCSAP.

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (0.77 mg/kg bm/day; USEPA, 2005c), the geometric mean of reproductive, growth, and survival NOAELs (2.3 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (7.1 mg/kg bm/day). All three TRVs are based on multiple

studies. However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that provides a level of protection most consistent with a minimal to low level of effects. Therefore, the most conservative TRV (0.77 mg/kg bm/day; USEPA, 2005c) was selected as a default TRV. The one key limitation with the selected TRV is that it may be overly conservative, especially when considering that only 5 of the 81 LOAELs in the USEPA dataset for reproduction, growth, or survival were below this TRV of 0.77 mg/kg bm/day.

Suggestions for improved future TRVs

Dose-response data from studies in the USEPA dataset could be further investigated to derive improved TRVs with a more quantified level of protection. This step, although likely an intense effort, would be an improvement on the USEPA TRV, which is based on a NOAEL and therefore considered potentially overly conservative. This step would likely lead to derivation of a TRV that is more aligned with FCSAP TRV guidance (FCSAP, 2010b) and that can be more quantitatively demonstrated to provide an appropriate level of protection. However, the selected TRV is considered likely to provide a sufficient level of protection and to be associated with no more than minimal to low effects to common species. The comprehensive methodology used to arrive at this TRV therefore makes it the best choice for a default FCSAP TRV at this time.

Chromium (hexavalent) [Metal]

Receptor: Mammals

Selected TRV = 9.24 mg/kg bm/day
Source: USEPA, 2008
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset and is the geometric mean of 21 NOAELs (from 20 studies) for reproduction and growth. Of these NOAEL data points, approximately half (11 out of 21) were bound by LOAELs. The studies considered only mouse and rat data, as mammalian toxicity data for hexavalent chromium are limited.

Merits of the selected TRV

The USEPA dataset includes substantially more toxicity data than other TRV derivation methods and, in this case, 20 studies were considered. All of the NOAELs used to calculate the geometric mean represented appropriate biological endpoints (growth and reproduction), and half were bound by LOAELs. No allometric scaling or uncertainty factors were used, and toxicity tests were determined to be representative of actual conditions. The depth of data considered in the development of this TRV better reflects the broad range of environmental exposure conditions and receptors than a TRV derived from single toxicological study.

Limitations of the recommended default TRV

The TRV study database only included studies on rats and mice, so it is uncertain if the TRV adequately represents all mammals. However, since none of the other TRVs considered mammals other than rats or mice, this issue is not a determining factor in default TRV selection. Another limitation is that USEPA uses a NOAEL approach, so there is potential that this TRV is overly conservative for FCSAP purposes. Chromium speciation in terrestrial ecosystems is complex and depends on many site-specific factors, including soil pH, organic matter content, and presence of other metal ions (CCME, 1999b). Therefore, where chromium is being investigated, consideration of the chromium speciation on a site-specific basis may be warranted.

Evaluation of candidate TRVs

Table A.4. Candidate mammalian toxicity reference values (TRVs) for hexavalent chromium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
3.28	Sample *et al.*, 1996
3.6	CEAEQ, 2012
9.24	**USEPA, 2008; Dillon, 2013**
13.14	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four TRVs were evaluated for hexavalent chromium, ranging between 3.28 and 13.14 mg/kg bm/day. Three of the TRVs were based on a single study (3.28, 3.6, and 13.14 mg/kg bm/day) and, for that reason, were not preferred to the USEPA TRV, which was based on a broader dataset. These three

single-study-based TRVs also had other limitations. None of the three provide quantitative information regarding their associated level of protection, leading to either potentially over- or under-protective assessments. The higher TRV from Sample *et al.* (1996; 13.14 mg/kg bm/day) was based on a single LOAEL for survival. Although this subchronic LOAEL was converted to a chronic LOAEL by multiplying by an uncertainty factor (of 0.1), there was no additional information about the effect size associated with this LOAEL. Therefore, the level of protection provided by this TRV is uncertain. Similarly, the lower TRV from Sample *et al.* (1996; 3.28 mg/kg bm/day) is based on an unbound NOAEL for growth and food consumption and therefore may potentially be overly protective. The CEAEQ (2012; 3.6 mg/kg bm/day) is also derived from a NOAEL (mortality), multiplied by an uncertainty factor (of 0.1) to account for the more severe survival endpoint. CEAEQ (2012) also applied allometric scaling (rat to mouse) in the derivation of this TRV, which is typically no longer recommended for TRV development (FCSAP, 2010b). None of these three TRVs were selected as a default for FCSAP given these various limitations (e.g., single study, lack of effect size) and given the availability of another TRV that met more of the evaluation criteria laid out in **Appendix B**.

The USEPA (2008) dataset overall includes 71 results from 20 papers for a range of endpoints. The USEPA TRV (9.24 mg/kg bm/day) is the geometric mean of 21 NOAELs for reproduction and growth from the USEPA dataset. Therefore, USEPA likely provides a more complete picture of mammalian toxicity to hexavalent chromium, compared to the three other candidate TRVs, which were all based on a single study. The main limitation of the USEPA TRV is that it might be overly conservative, and there is no quantitative evaluation available at this time on the level of protection provided by this TRV. However it is within the range of other available TRVs that were evaluated, it is derived considering the results from multiple toxicity studies and, overall, it is considered to be associated with no more than minimal to low effects to common species, thus providing an appropriate level of protection as a default TRV for FCSAP. One uncertainty regarding this TRV pertains to chromium speciation. Hexavalent chromium is considered more toxic than trivalent chromium. Hexavalent chromium is primarily from anthropogenic sources, whereas trivalent chromium is more likely to occur naturally (CCME, 1999b). Chromium speciation (as hexavalent chromium, trivalent chromium, or other) is dependent on site conditions. Where chromium is a contaminant on a site, it would also be useful to collect site-specific information on chromium speciation in the terrestrial environment to reduce this uncertainty in ERAs.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying the selected NOAEL-based TRV and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV with a quantitatively calculated level of protection. Chromium toxicity has been much more extensively studied in the context of human health relative to the wildlife toxicity context (CCME, 1999b). It is suspected that the toxicity data underlying human health TRVs may also be relevant to mammalian wildlife toxicity and, therefore, there may be potential to consider additional data from human-health-based TRVs for development of future wildlife TRVs.

Chromium (total) [Metal]

Receptor: Mammals

Selected TRV = 2.4 mg/kg bm/day
Source: USEPA, 2008
Grade: C

Basis for the selected TRV

The selected TRV is from an USEPA dataset (2008) and is the geometric mean of nine NOAELs (all unbound) for growth endpoints from eight unique studies (there were no NOAELs for reproduction available in the dataset to include in the calculation of this geometric mean). The USEPA 2008 dataset also included an additional six unbound LOAELS for survival, growth, or reproduction endpoints and one unbound NOAEL for a survival endpoint, which were not directly included in the geometric mean, as per the USEPA (2003) methodology for TRV derivation. Data from the USEPA 2008 dataset contained studies on four species of mammals, namely pig, cattle, rat and mouse. These species account for a moderate representation of all mammals. However, the addition of other species (particularly more sensitive species) could strengthen the dataset considerably. Note that trivalent chromium is the chemical form used in underlying toxicity tests, on the assumption that the majority of total chromium is trivalent form.

Merits of the selected TRV

The USEPA TRV was derived from multiple toxicological studies (n = 9) and therefore reflects the broad range of exposure conditions and receptors more so than a TRV derived from a single toxicological study. Four species of mammals were tested in the studies, which provides a broader representation of a variety of mammals compared to TRVs derived from only rat and/or mouse toxicity data. The study was well designed (acceptable biological endpoints; reflective of actual environmental conditions; range of exposure times; exposure pathway through contaminated food and water) and no allometric scaling or uncertainty factors were applied during TRV derivation.

Limitations of the recommended default TRV

Overall, limited data are available for trivalent chromium in the literature. As a result, the USEPA chromium (total) TRV dataset only included studies with unbound NOAELs, with growth as the biological endpoint. Bound NOAELs are preferred because they provide a more detailed picture of the dose-response relationship. Also, TRVs derived from NOAELs can often be overly conservative for FCSAP purposes. Other indications that the selected TRV is potentially overly conservative are that it is the lowest of all of the evaluated candidate TRVs (Table A.5) and that there were no LOAELs (for reproduction, growth, or survival) in the USEPA dataset that were found to be below the selected TRV. Confidence in the selected TRV for total chromium (2.4 mg/kg bm/day) is also low because it is lower than the selected TRV for hexavalent chromium (9.24 mg/kg bm/day), which is thought to be more toxic. Trivalent chromium can be present from natural sources (CCME, 1999b). Hexavalent chromium on the other hand is primarily from anthropogenic sources (CCME, 1999b). Chromium speciation in terrestrial ecosystems is complex and depends on many site-specific factors, including soil pH, organic matter content, and presence of other metal ions (CCME, 1999b). Therefore, where chromium is being investigated, and especially where sources of hexavalent chromium contamination are suspected, site-specific consideration of chromium speciation is warranted. Additional concerns with an overly conservative TRV stem from the fact that trivalent chromium is a micronutrient. However, trivalent

chromium or total chromium doses associated with minimum required daily intakes were not reviewed as part of this evaluation.

Evaluation of candidate TRVs

Table A.5. Candidate mammalian toxicity reference values (TRVs) for total chromium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
2.4	**USEPA, 2008; Allaway and Stodola, 2011; Dillon, 2013**
3.6	CEAEQ, 2012
5.5	OMOE, 2011; Allaway and Stodola, 2011
9.6	OMOE, 2011; Allaway and Stodola, 2011
2737	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Five TRVs for total chromium, spanning over three orders of magnitude from 2.4 to 2737 mg/kg bm/day, were evaluated. The lowest value of 2.4 mg/kg bm/day was selected (from USEPA, 2008) as the default TRV because of the merits described above. The third lowest TRV (5.5 mg/kg bm/day; OMOE, 2011) was based on an NOAEL for histopathological changes in dogs and cats. OMOE (2011) also included a TRV of 9.6 mg/kg bm/day, which was based on a LOAEL for kidney damage in cows. The two TRVs from OMOE (2011) were not selected as default TRVs for FCSAP because they were intended to protect specific categories of animals (5.5 mg/kg bm/day for protection of red fox; 9.6 mg/kg bm/day for protection of sheep). Therefore, these two TRVs have uncertain application as a default value to protect all mammal species. Furthermore, there was insufficient information readily available to fully evaluate both of these TRVs. The TRV from CEAEQ (2012; 3.6 mg/kg bm/day) was based on a NOAEL for survival, multiplied by an uncertainty factor (0.1) to account for the mortality endpoint, and included allometric scaling (rat to mouse). The CEAEQ (2012) TRV was selected as the lowest NOAEL (growth, reproduction, or mortality endpoints) from three separate studies, two of which tested the toxicity of hexavalent chromium and only one of which tested the toxicity of trivalent chromium. Therefore, the TRV from CEAEQ (2012; 3.6 mg/kg bm/day) has uncertain application as a default TRV for total chromium. The highest available TRV (2737 mg/kg bm/day) from Sample *et al.* (1996) is over three orders of magnitude greater than the selected TRV and is based on an unbound NOAEL for 90-day reproduction and 2-year cancer and longevity. Each TRV, including the selected TRV, has its own merits and limitations based on the criteria applied in this evaluation. Further investigation is warranted to address the large range across available TRVs.

Suggestions for improved future TRVs

In general, limited mammalian toxicological data is available for trivalent chromium. However, the utility of this data could be improved by calculating the effects size of the available NOAEL/LOAEL data and subsequently applying recommended FCSAP TRV derivation methodology (FCSAP, 2010b) that is integrative of data across multiple studies (rather than trying to identify a single "best" study or TRV). Consideration of a mammal's minimum required daily doses for total and/or trivalent chromium could be included as a part of future TRV derivation. Additionally, updated literature searches for additional toxicology data may help supplement the currently limited set of available data.

Copper [Metal]

Receptor: Mammals

Selected TRV = 5.6 mg/kg bm/day
Source: USEPA, 2007a
Grade: A

Basis for the selected TRV

The selected TRV is from USEPA (2007a) as the highest bound NOAEL below the lowest bound LOAEL for relevant biological endpoints (reproduction, growth, and survival) in a large dataset (278 results from 97 studies). The particular study corresponding to this NOAEL is Allcroft *et al.* (1961). Overall, the study dataset included multiple mammalian species (rat, mouse, pig, mink, cattle, guinea pig, rabbit, horse, shrew, sheep and goat) and is therefore considered to be representative of all mammals.

Merits of the selected TRV

The selected TRV is the only candidate mammalian copper TRV (Table A.6) that included more than one study in its derivation methodology. In total, 97 studies were assessed for this TRV, which spanned several different species of mammals and relevant biological endpoints. Other merits of the selected TRV are that no allometric scaling or uncertainty factors were applied and that the experimental design is reflective of actual environmental conditions because of the exposure pathways of contaminated food and water, relevant chemical forms (copper sulfate, copper chloride, cupric carbonate, and copper acetate), and a range of acute and chronic exposure durations (15 days to 2 years).

Limitations of the recommended default TRV

The main limitation of this TRV is that it employed LOAEL/NOAEL methods instead of dose-response, and the majority of the NOAELs in the USEPA study were unbound (91/123). Because USEPA derives a NOAEL-based TRV, there is potential that it is overly conservative for the FCSAP program. However, four LOAELs for reproduction, growth or survival in the USEPA study were found to be below the selected TRV. Additionally, all bound NOAELs were found to be, on average, a factor of two or less than their corresponding LOAEL. This potentially indicates a steep dose-response curve and, therefore, this NOAEL-based TRV is considered likely to provide a sufficient level of protection as a default value for FCSAP sites (although further quantitative analysis would be required to support the level of protection provided by this TRV). Although the USEPA dataset does include three studies for sheep, there may be a need to derive, on a site-specific basis, more receptor- and site-specific TRVs where sheep are a receptor of concern. Sheep are considered to be a more sensitive receptor to copper exposure, as well as to complex interactions between copper and other elements, resulting in a narrow dose-range between copper deficiency and copper toxicity (CCME, 1999c).

Evaluation of candidate TRVs

Table A.6. Candidate mammalian toxicity reference values (TRVs) for copper

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.89	OMOE, 2011; Allaway and Stodola, 2011
5.6	**USEPA, 2007a; Dillon, 2013**
15.14	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
26.67 [2]	USEPA Region 9 BTAG, 2009
30.7	CEAEQ, 2012
38	Rae, 2013
74	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.
2. This value represents the "unadjusted dose" (i.e., without uncertainty factors), as presented in USEPA Region 9 BTAG (2000). The USEPA Region 9 BTAG (2009) mammalian TRV for copper is 2.67 mg/kg bm/day, which includes an uncertainty factor of 10 for subchronic to chronic conversion.

A total of seven copper mammalian TRVs, ranging from 0.89 to 74 mg/kg bm/day, were evaluated by FCSAP. The 0.89 and 26.67 mg/kg bm/day TRVs could not be selected as default values because insufficient information was available to fully assess their derivation methods, which results in a high degree of uncertainty associated with these TRVs. Two of the remaining TRVs (15.4 mg/kg bm/day, Sample *et al.*, 1996; and, 30.7 mg/kg bm/day, CEAEQ, 2012) were based on single toxicological studies. Therefore, these TRVs do not incorporate any information about the range of doses associated with adverse effects across a broader range of species, endpoints, or exposure conditions, as is relevant for a default value for FCSAP. Furthermore, neither of these TRVs reported an associated quantitative level of effect, and therefore the level of protection provided by these TRVs is uncertain. In particular, the Sample *et al.* (1996) TRV of 15.4 mg/kg bm/day is based on a LOAEL for reproduction (mink exposed to copper in their diet for 1 year), which may have the potential to exceed a level of protection consistent with a minimal to low level of effects to populations of common species.

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (5.6 mg/kg bm/day; USEPA, 2007a), the geometric mean of reproductive, growth, and survival NOAELs (38 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (74 mg/kg bm/day). All three TRVs are based on multiple studies and included data across a broad range of species (rat, mouse, pig, mink, cattle, guinea pig, rabbit, horse, shrew, sheep, goat), endpoints, and exposure conditions. However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that provides a level of protection most consistent with a minimal to low level of effects. The most conservative of the three TRVs (5.6 mg/kg bm/day; USEPA, 2007a) was thus selected as a default FCSAP TRV.

Suggestions for improved future TRVs

Dose-response data from studies in the USEPA dataset could be further investigated to derive improved TRVs with a more quantified level of protection. This step, although likely an intense effort, would be an improvement on the USEPA TRV, which is based on a NOAEL and is therefore considered potentially overly conservative. This step would likely lead to derivation of a TRV that is more aligned with FCSAP TRV guidance (FCSAP, 2010b) and that can be more quantitatively demonstrated to

provide an appropriate level of protection. However, the selected TRV is considered likely to provide a sufficient level of protection and to be associated with no more than minimal to low effects to common species, and the comprehensive methodology used to arrive at this TRV makes it the best choice for a default FCSAP TRV at this time.

Free Cyanide [Inorganic]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the candidate TRVs were considered appropriate as default values for FCSAP.

Table A.7. Candidate mammalian toxicity reference values (TRVs) for cyanide

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.96	CCME, 1996b; Allaway and Stodola, 2011; Dillon, 2013; OMOE, 2011
1.97	CCME, 1996b; Allaway and Stodola, 2011
2.23	CCME, 1996b; Allaway and Stodola, 2011
2.31 to 3.27	CCME, 1996b; Allaway and Stodola, 2011
23.0	Dillon, 2013
68.7	Sample *et al.*, 1996; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Several TRVs, ranging from 0.96 to 68.7 mg/kg bm/day, were evaluated, but none were considered suitable for FCSAP. All available TRVs were based on experiments that tested single, one-time exposures, which are not representative of continuous long-term environmental exposures at federal contaminated sites. Three TRVs from CCME (1996b, as cited in Allaway and Stodola, 2011), ranging from 1.97 to 3.27 mg/kg bm/day, were based on a minimum lethal dose, which is considered too severe a level of effect for a default FCSAP TRV. However, the lowest available TRV at a dose of roughly half the minimum lethal dose (0.96 mg/kg bm/day; CCME, 1996b, based on Clawson *et al.*, 1934) was based on a LOAEL for respiratory stress. The proximity in values (factor of 2) between TRVs based on lethal and sub-lethal (i.e., respiratory stress) endpoints contributes to low confidence in selecting either one as a default for FCSAP. There were several major concerns with all available TRVs, including experimental design (e.g., exposure duration), TRV derivation methodology (use of uncertainty factors), and inappropriate endpoints or effect sizes. Furthermore, the range reported by CCME (1997b) to be associated with acute mammalian cyanide poisoning (0.5 to 3.5 mg/kg bm) falls below several of the TRVs, indicating that even the lowest available TRV may not provide adequate protection for FCSAP goals.

Suggestions for improved future TRVs

On the basis of the criteria established for this project, none of the available candidate TRVs were considered appropriate or sufficient for FCSAP. Given the high degree of uncertainty and limitations associated with the available TRVs and the overall limited amount of toxicity data for mammalian cyanide toxicity, further investigation is recommended to develop a default TRV that is appropriate for FCSAP. Future steps should include performing a search for any new or updated toxicity data and applying more current TRV derivation methods to take advantage of the limited toxicity data that are available. For example, the following sources include additional TRVs that could be reviewed: (1) Health Canada's Cyanide document (1991), which cites potentially relevant chronic toxicity data, including a 2-year study with rats (no effects at 7.5 or 10.8 mg/kg bm/day; Gettler and Baine, 1938); and (2) a CCME soil quality guideline fact sheet (1997b), which cites a chronic oral reference dose of 0.02 mg/kg bm based on Howard and Hanzal (1955).

Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Lead [Metal]

Receptor: Mammals

Selected TRV = 4.7 mg/kg bm/day
Source: USEPA, 2005d
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 219 studies and is the highest bound NOAEL below the lowest bound LOAEL. Studies in the database included toxicity tests conducted on a variety of mammalian species, including rat, sheep, guinea pig, hamster, cattle, dog, shrew and pig. Thus, the selected TRV is deemed representative of a broad range of mammalian species. Biological endpoints assessed in toxicity tests across the dataset include reproduction, growth and mortality.

Merits of the selected TRV

The TRV selected through the USEPA derivation process comes from Kimmel *et al.* (1980). This particular toxicological study did not employ allometric scaling or uncertainty factors in deriving the TRV. Additionally, the USEPA data was the only lead mammalian TRV reviewed by FCSAP that utilized more than a single study in the TRV derivation process. In fact, the USEPA TRV was based on 271 toxicological studies using a wide variety of mammalian species, whereas the other TRVs used only rats and/or mice as their test species. USEPA also considered a number of relevant biological endpoints, and the depth of data considered in the development of this TRV therefore better reflects a broad range of environmental exposure conditions and receptors, compared to a TRV derived from a single toxicological study.

Limitations of the recommended default TRV

The quantitative level of protection provided by this TRV is uncertain. The USEPA (2005d) may potentially be overly conservative, based on a variety of indicators: (i) it uses a NOAEL-based approach to derive TRVs (NOAELs are a more conservative metric of effects); (ii) only approximately half of the NOAELs included in this TRV's derivation were bound with LOAEL data; and (iii) only 9 of the 151 LOAELs for reproduction, growth and survival in the USEPA dataset are lower than 4.7 mg/kg bm/day, the selected lead mammalian TRV, indicating that adverse effects potentially occur infrequently below the TRV. Therefore, the effect size and level of protection provided by this TRV is uncertain. Lead acetate, the chemical form used in the majority of the laboratory-based toxicological studies, is a highly soluble form of lead and may contribute to an overly conservative level of protection provided by this TRV. It may be possible, on a site-specific basis, to apply methods and tests that are intended to assess bioavailability of contaminants like lead and then to incorporate site-specific and ecologically relevant chemical uptake and exposure information into an ERA.

Evaluation of candidate TRVs

Table A.8. Candidate mammalian toxicity reference values (TRVs) for lead

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
4.7	**USEPA, 2005d; Dillon, 2013**
22.4	Allaway and Stodola, 2011
47	Rae, 2013
80	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
161.6	CEAEQ, 2012
170	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Six TRVs, ranging from 4.7 to 170 mg/kg bm/day, were evaluated by FCSAP. Three of these TRVs (22.4 mg/kg bm/day, Allaway and Stodola, 2011; 80 mg/kg bm/day, Sample *et al.*, 1996; and, 161.6 mg/kg bm/day, CEAEQ, 2012) could not be selected as default values for FCSAP because it was not immediately clear from the primary literature whether they provide a sufficient level of protection for a default TRV for FCSAP. All three of these TRVs were based on a reproductive LOAEL in rats from Azar *et al.* (1973), and the effect size associated with the LOAELs underlying these three TRVs is not readily clear. Furthermore, because these TRVs are based on a single study, they do not allow an evaluation of where they fit within the distribution of doses associated with adverse effects across a broad range of species, endpoints, or exposure conditions, as is relevant for FCSAP default TRVs.

The remaining three TRVs are from the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (4.7 mg/kg bm/day; USEPA, 2005d), the geometric mean of reproductive, growth, and survival NOAELs (47 mg/kg bm/day; Rae, 2013), and the geometric mean of reproductive, growth, and survival LOAELs (170 mg/kg bm/day). All three of these TRVs are based on multiple studies and are intended to evaluate no to low-level effects. However, they are each an order of magnitude apart. None of the three provide a quantitative measure of the level of effect that they represent. So, in light of the broad range of the three TRVs and in the absence of a quantitative method for selecting the TRV that best provides a level of protection that is consistent with a minimal to low level of effects (<20% effect), the most conservative TRV (4.7 mg/kg bm/day; USEPA, 2005d) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying the selected NOAEL-based TRV and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV with a quantitatively informed level of protection. This step is likely to be especially valuable for resolving the large discrepancy between the three TRVs that are all ultimately based on the same underlying toxicological data.

Mercury, inorganic [Metal]

Receptor: Mammals

Selected TRV = 5.8 mg/kg bm/day
Source: CEAEQ, 2012
Grade: B

Basis for the selected TRV

The selected TRV is from CEAEQ (2012) and was derived from a single study (Aulerich *et al.*, 1974) that exposed mink to a single experimental dose level (10 ppm) of mercuric chloride through their diets for 6 months. This experimental dose level was associated with 9% reduced birthweight in baby mink. The selected TRV of 5.8 mg/kg bm/day was calculated by extrapolating an EC_{20} for that same reproductive endpoint and applying allometric scaling to convert the dose from mink to an equivalent dose for a mouse.

Merits of the selected TRV

Aulerich *et al.* (1974) exposed minks to mercuric chloride through their diets for 6 months, which is moderately reflective of actual environmental conditions (exposure duration and pathway). The assessment endpoint was reproductive (mink kit weight), which represents an acceptable biological endpoint that can be more readily applied to population-level effects. There is a quantitative effect level (20%) associated with this TRV, which confirms that this TRV is supportive of intended level of protection for default wildlife TRVs for FCSAP (i.e., no more than minimal to low level of effects to common species). No uncertainty factors were used in the derivation of this TRV.

Limitations of the recommended default TRV

Overall, there is limited toxicity data available for inorganic mercury, in contrast to organic mercury (i.e., methylmercury), which is toxicologically the most relevant form of mercury (CCME, 2000). Consult other sources (e.g., CCME, 2000) for evaluating wildlife risks to methylmercury, as the organic form of mercury is not considered in this TRV.

The selected TRV for inorganic mercury is derived from a single study, testing a single experimental dose level (10 ppm) for a single species (mink), which means that its application and extrapolation to a broader set of exposure conditions, other dose levels, and other mammalian species is uncertain. Furthermore, although it is not within the scope of this module to review human-health-based TRVs as candidates for default FCSAP wildlife TRVs, given the limited number of available inorganic wildlife TRVs, it is also worth noting that CCME (1999d) identifies rat-based LOAELs ranging from 0.226 to 0.633 mg/kg bm/day; these values may be considered further in site-specific TRV selection and use.

The selected default TRV also applied allometric scaling to convert from a mink-based dose to a mouse-equivalent. This is not consistent with current preferred methodology for TRV development (FCSAP, 2010b), which discourages the use of allometric scaling.

Evaluation of candidate TRVs

Table A.9. Candidate mammalian toxicity reference values (TRVs) for inorganic mercury

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
1	Sample *et al.*, 1996; Allaway and Stodola, 2011; Dillon, 2013
5.8	**CEAEQ, 2012**
13.2	Sample *et al.*, 1996

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

All three of the evaluated TRVs were based on a single study for a single species (rat or mink), with similar exposure durations and pathways (inorganic mercury in the diet for 6 months) and no uncertainty factors. Both the lowest TRV from Sample *et al.* (1996; 1 mg/kg bm/day) and the selected TRV from CEAEQ (2012; 5.8 mg/kg bm/day) were based on the same underlying toxicological study (Aulerich *et al.*, 1974) with mink. The difference between these two TRVs is that Sample *et al.* (1996) directly used the unbound NOAEL (associated with 9% effect level), whereas CEAEQ (2012) extrapolated from the toxicity data a dose associated with a 20% effect level and applied allometric scaling. The higher Sample *et al.* (1996) TRV of 13.2 mg/kg bm/day was not selected as a default for FCSAP because of major concerns associated with the insoluble chemical form of mercury (mercuric sulfide) used in the underlying toxicity test (Revis *et al.*, 1989) with rats. The form of the metal is very important when evaluating a TRV for mercury, because the solubility (and therefore bioavailability) varies greatly between different ionic forms of mercury. No adverse effects were observed at any of the 30 dose levels applied by Revis *et al.* (1989), likely because the mercuric sulfide in the food was not very bioavailable to the test species, which would lead to this TRV potentially being under-protective for more bioavailable forms of inorganic mercury. For example, the other two candidate TRVs (1 and 5.8 mg/kg bm/day) are based on the more soluble and bioavailable divalent mercury ($HgCl_2$). Until more specific TRVs are developed for different inorganic forms of mercury, the default value developed from the more bioavailable, soluble form of inorganic mercury could be applied to all forms of inorganic mercury, noting that it would likely be over-protective for less soluble forms, such as monovalent mercury in mercuric sulfide.

Suggestions for improved future TRVs

Very limited toxicity data was available for inorganic mercury in this evaluation. A literature search for any potential additional toxicological data would therefore likely benefit future TRVs. For example, the USEPA Great Lakes Water Quality Initiative (GLWQI) for Protection of Wildlife (USEPA, 1995) cites additional toxicity data for inorganic mercury toxicity, including a NOAEL of 14 mg/kg bm/day for reproduction and development (Fitzhugh *et. al.,* 1950) and a LOAEL of 7 mg/kg bm/day for development (Rizzo and Furst, 1972). These data were presented in USEPA 1995) as part of literature search results; they were not directly used to derive TRVs nor were they presented as wildlife TRVs (the GLWQI did derive wildlife TRVs focused on organic mercury). Therefore, these toxicity data from Rizzo and Furst (1972), as cited in USEPA (1995), were not evaluated as candidate TRVs in this module. They are presented here only as additional context for available wildlife TRVs and for possible consideration in site-specific applications of wildlife TRVs for organic mercury. In addition, further investigation into the currently available underlying toxicological data (i.e., dose-response data) and application of recommended TRV derivation methodology (FCSAP, 2010b) could quantitatively integrate and enhance the utility of the limited toxicity data available.

Nickel [Metal]

Receptor: Mammals

Selected TRV = 1.7 mg/kg bm/day
Source: USEPA, 2007b
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 119 studies and is the highest bound NOAEL below the lowest bound LOAEL for the reproductive, growth, and survival endpoints. The selected TRV (1.7 mg/kg bm/day) is from Pandey and Srivastava (2000), who studied reproductive effects in mice over 35 days. The USEPA dataset included data for five species (rat, mouse, dog, vole and cattle), and the TRV is therefore considered to be representative of a variety of mammals. However, it is ultimately based on a NOAEL at the lower limit of the range of NOAELs reported in that dataset and therefore may potentially be overly conservative as a default value for FCSAP.

Merits of the selected TRV

The selected TRV was the only mammalian nickel TRV evaluated by FCSAP that was based on more than one study (n=119). The inclusion of multiple studies means the dataset included multiple biological endpoints, multiple species and a range of study durations. Other merits of the selected TRV are that no allometric scaling or uncertainty factors were applied and that the study was deemed to be reflective of actual environmental conditions (i.e., dietary exposure pathway, chemical form, and study exposure period).

Limitations of the recommended default TRV

The selected TRV is based on a NOAEL, so it may be overly conservative for FCSAP purposes. However 7 (of 30) LOAELs for reproduction, growth, or mortality in the USEPA dataset are below the selected TRV, indicating that adverse effects may occur below the selected TRV. The effect size associated with these LOAELs and with the selected TRV is uncertain, and further investigation should therefore seek to quantify the level of protection provided by the selected TRV.

Evaluation of candidate TRVs

Table A.10. Candidate mammalian toxicity reference values (TRVs) for nickel

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
1.7	**USEPA, 2007b; Dillon, 2013**
11.2	Sample *et al.*, 1996; Allaway and Stodola, 2011
10	Rae, 2013
13	Rae, 2013
40	Allaway and Stodola, 2011
161.6	CEAEQ, 2012

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Six mammalian TRVs for nickel, ranging from 1.7 to 161.6 mg/kg bm/day, were evaluated. Two TRVs (11.2 and 40 mg/kg bm/day) were based off a bound NOAEL for offspring growth from the same

underlying toxicological study (Ambrose *et al.*, 1976). Sample *et al.* (1996) and Allaway and Stodola (2011) arrived at different TRVs values due to allometric scaling being used to convert rat toxicity data (40 mg/kg bm/day) to white-tailed deer (11.2 mg/kg bm/day). The TRV from CEAEQ (2012; 161.6 mg/kg bm/day) is also based off a single toxicity study—in this case, a bound LOAEL for a reproductive endpoint (reduced baby rat weight) in rats exposed to nickel in their diet for three generations. For all three of these TRVs based on single studies, their relevance to a broader range of mammals and exposure conditions is uncertain, and their associated effect levels are not quantified because they are based on a NOAEL or LOAEL.

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (1.7 mg/kg bm/day; USEPA, 2007b), the geometric mean of reproductive, growth, and survival NOAELs (10 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (13 mg/kg bm/day). All three TRVs are based on multiple studies (48 NOAELs and 30 LOAELs for reproduction, growth, or survival). However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that best provides a level of protection of no more than minimal to low effects. Therefore, the most conservative TRV (1.7 mg/kg bm/day; USEPA, 2007b) was selected as a default FCSAP TRV.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying the selected NOAEL-based TRV and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV associated with a quantitative level of effect. This step is likely to be especially valuable for improving TRVs that, like the selected default TRV, are based on a relatively small dataset (48 NOAELs and 30 LOAELs) and can therefore be more sensitive to outliers.

Selenium [Metalloid]

Receptor: Mammals

Selected TRV = 0.143 mg/kg bm/day
Source: USEPA, 2007c
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 132 studies and is the highest bound NOAEL that is lower than the lowest bound LOAEL. The result is a NOAEL-based TRV from Mahan and Moxon (1984). The USEPA dataset includes multiple species of mammals, including pig, rat, cattle, mouse, sheep, hamster, dog and rabbit, with multiple biological endpoints (reproduction, growth and survival).

Merits of the selected TRV

The USEPA TRV was derived from more than one study (n= 132) and more than one species (n=8) in its derivation methodology. This includes sheep, which are considered to be the "most sensitive mammalian species to Se intoxication" by CCME (2009). Derivation of the selected TRV utilized relevant biological endpoints, and no allometric scaling or uncertainty factors were applied.

Limitations of the recommended default TRV

The USEPA dataset includes many unbound NOAELs, and therefore this TRV may potentially be overly conservative. In fact, only 4 of 163 LOAELs for reproduction, growth and survival in the USEPA (2007c) dataset are less than the NOAEL-based USEPA (2007c) TRV. Some uncertainty exists as to whether the studies included in the dataset are reflective of actual field conditions because inorganic forms of selenium (e.g., sodium selenite) were used in the majority of the studies, as opposed to the more bioavailable organic forms (e.g., selenomethionine). Additionally, the maximum study duration within the USEPA (2007c) dataset was 180 days and no second generation-level effects were taken into account, which may be relevant considerations in ERA scenarios.

Evaluation of candidate TRVs

Table A.11. Candidate mammalian toxicity reference values (TRVs) for selenium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.05	USEPA Region 9 BTAG, 2009
0.08	CCME, 2009; OMOE, 2011
0.143	**USEPA, 2007c; Dillon, 2013**
0.33	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
0.51	CEAEQ, 2012
0.54	Rae, 2013
0.8	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Seven TRVs, ranging from 0.05 mg/kg bm/day to 0.8 mg/kg bm/day, were evaluated. The lowest TRV (0.05 mg/kg bm/day; USEPA Region 9 BTAG, 2009) could not be selected for a number of reasons, including insufficient information in either USEPA Region 9 BTAG (2009) or in the original underlying

toxicity study (Harr *et al.*, 1967) for a complete evaluation of its suitability as a default TRV for FCSAP. The second-lowest TRV (0.08 mg/kg bm/day; CCME, 2009) was reported in CCME (2009) as a lowest effect dose available for sheep from a toxicity study by Puls (1994) which exposed sheep to selenium in the diet for 1 year. CCME (2009) rejected this 0.08 mg/kg bm/day TRV for developing a daily threshold effect dose (DTED) because of the lack of available information about this dose level (e.g., unknown chemical form of selenium, unknown endpoint). The evaluation for the purposes of selecting a default value for FCSAP also determined that the lack of information prevents the selection of this 0.08 mg/kg bm/day TRV as a default wildlife TRV for FCSAP. This same dose of 0.08 mg/kg bm/day was also reported as the maximum tolerable dietary level for selenium that is protective of domestic animals (NAS, 1976 and 1980). The 0.33 mg/kg bm/day TRV from Sample *et al.* (1996) was also not selected because it does not provide an adequate level of protection; there was a 50% reduction in females' production of second- generation young in the toxicity test underlying this TRV from Sample *et al.* (1996), which is too severe to provide a level of protection that is consistent with only a minimal to low level of effects. The TRV from CEAEQ (2012; 0.51 mg/kg bm/day) is also based on the same underlying toxicity data as the Sample *et al.* TRV (1996; 0.33 mg/kg bm/day), except that allometric scaling was applied and a regression equation was applied to extrapolate an EC_{20} from the toxicity data. Even though a 20% quantified effect level is sufficient for a default wildlife TRV for FCSAP, the CEAEQ (2000) TRV was not selected because of uncertainties in applying a TRV extrapolated from only a single older (Rosenfeld and Beath, 1954) toxicity study and because of the application of allometric scaling, which is not consistent with current recommended methodology for TRV development (FCSAP, 2010b).

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (0.143 mg/kg bm/day; USEPA, 2007c), the geometric mean of reproductive, growth, and survival NOAELs (0.54 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (0.8 mg/kg bm/day). All three TRVs are based on multiple studies. However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that best provides a level of protection of no more than minimal to low effects. Therefore, the most conservative of these three TRVs (0.143 mg/kg bm/day; USEPA, 2007c) was selected as a default TRV for FCSAP, until a suitable TRV becomes available that applies a more quantitative dose-response methodology, as described in FCSAP (2010b).

Suggestions for improved future TRVs

Improvements to future TRVs (both future defaults for FCSAP, as well as site-specific TRVs) may be made by a quantitative evaluation of effect sizes associated with underlying toxicological data and application of recommended TRV derivation methodology (FCSAP, 2010b). Future TRV derivation could also include investigations into the bioaccumulation of selenium in mammals (especially in mammals in aquatic food webs) and into the implications of applying toxicity data based on inorganic selenium (generally less bioavailable than organic selenium) to a FCSAP TRV intended to be protective of all forms of selenium.

Thallium [Metal]

Receptor: Mammals

Selected TRV = 0.015 mg/kg bm/day
Source: Williams *et al.*, 2015
Grade: B

Basis for the selected TRV

The selected TRV is from Williams *et al.* (2015), who established an unbound LOAEL for sperm motility in male rats from a study by Formigli *et al.* (1986) as the basis for this TRV. Although sperm motility is not a typical endpoint for wildlife TRV derivation, Williams *et al.* (2015) justifies the use of this endpoint by relating it to reduced fertility, which in turn could potentially have population-level adverse effects. Formigli *et al.* (1986) reported a significant decrease in fertility when sperm motility was 37% or less. The selected TRV is based on an unbound LOAEL for reduced sperm motility from Formigli *et al.* (1986) (40% sperm motility at LOAEL, compared to 66.5% motility in control, for 40% reduced sperm mobility). Therefore, there is the potential for significantly reduced fertility, and the implications of this reproductive endpoint for wildlife populations should be considered on a site-specific basis. The severity of the potentially reduced fertility is unknown, and the use of an uncertainty factor further obscures the effect size associated with this selected TRV.

Merits of the selected TRV

Williams *et al.* (2015) considered seven different studies for thallium toxicity to mammals, reporting a variety of endpoints (including mortality, growth, and others) and species (rat, mouse, hamster, and guinea pig) before selecting the LOAEL from Formigli *et al.* (1986). Rats were exposed to thallium through drinking water, a relevant exposure pathway, for a 60-day duration.

Limitations of the recommended default TRV

The selected TRV is inconsistent with FCSAP TRV derivation guidance because the LOAEL (for sperm-motility) was divided by an uncertainty factor of 20 to calculate a NOAEL. There is uncertainty about the effect size associated with this TRV based on a sperm-mobility endpoint and therefore about the level of protection provided to mammalian species.

Evaluation of candidate TRVs

Table A.12. Candidate mammalian toxicity reference values (TRVs) for thallium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.015	**Williams *et al.*, 2015**
0.07	Sample *et al.*, 1996; Dillon, 2013
0.075	Williams *et al.*, 2015
0.2	OMOE, 2011; Allaway and Stodola, 2011
0.48	USEPA Region 9 BTAG, 2009

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Five TRVs, ranging from 0.015 to 0.48 mg/kg bm/day, were evaluated. Two of the TRVs (0.07 and 0.48 mg/kg bm/day) were not considered appropriate as a default for FCSAP because of uncertainties related to derivation methods (e.g., unclear use of allometric scaling or uncertainty factors), relevance of toxicity test conditions to environmental conditions, and level of protection sufficient to provide no more than minimal to low level of effects. The TRV from OMOE (2011; 0.2 mg/kg bm/day) was derived from an unbound NOAEL for an unconventional endpoint (alopecia) in one study (Stoltz *et al.*, 1986, as cited in CCME, 1999e) with rats. There were several limitations associated with this TRV from OMOE, including uncertain relevance of this endpoint for the protection of mammalian populations, the fact that gavage exposure pathway is not representative of environmental exposure pathways, consideration of only one toxicity study, and a potentially overly conservative level of protection. The 0.075 mg/kg bm/day TRV from Williams *et al.* (2015) has all the same qualities, merits, and limitations as the selected TRV, except that it included a less conservative uncertainty factor of 4 (to account for subchronic exposure duration), compared to the uncertainty factor of 20 incorporated into the selected TRV. The more conservative TRV from Williams *et al.* (2015) was selected because, given the uncertainties in effect size associated with both TRVs, the lower value is more likely to meet targeted FCSAP default TRV protection levels.

Suggestions for improved future TRVs

Overall, mammalian toxicity data for thallium is limited. For contaminated sites where thallium is a concern, further investigation of the toxicity data underlying existing TRVs, a literature review for any potential additional and/or more recent toxicological data, and application of dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014) will help refine evaluations of ecological risks to mammals from exposure to thallium and may lead to the derivation of improved TRVs in the future.

Uranium [Metal]

Receptor: Mammals

Selected TRV = 6.13 mg/kg bm/day
Source: Sample *et al.*, 1996
Grade: B

Basis for the selected TRV

The TRV is from Sample *et al.* (1996), who used data from a toxicity study by Paternain *et al.* (1989). This TRV is based on a bound LOAEL for reproductive endpoints in mice (number of dead young per litter and size and weight of offspring). In this study, mice were exposed to uranyl acetate (61.32% U) via oral intubation; male mice were exposed for 60 days prior to mating and female mice were exposed for 15 days prior to mating, as well as throughout mating, gestation, delivery, and nursing of the litters.

Merits of the selected TRV

The selected TRV is based on a relevant reproductive endpoint. No allometric scaling or uncertainty factors were applied to underlying toxicity data to calculate this TRV. The dose level of this selected TRV is associated with less than 25% reduction in reproductive endpoints (Paternain *et al.*, 1989), which is considered to be consistent with a minimal to low level of effect on common species. Two reproductive endpoints were reported as significantly different from control at 6.13 mg/kg bm/day: number of dead young per litter and body mass of pups, on days 4 and 21 after birth. The weights of pups in the 6.13 mg/kg bm/day treatment level were reduced by 10% and 9% relative to control on days 4 and 21 respectively. Although it was not possible to normalize the other endpoint (number of dead young per litter), there was one dead young/litter (SD= 2.2) at birth (day 0) in the 6.13 mg/kg bm/day treatment level, compared to 0 dead pups per litter in the control.

Limitations of the recommended default TRV

The selected TRV is based on a single study with mice. Therefore, limitations of this selected TRV include uncertain applicability to other mammals and exposure conditions. The selected TRV is based on a single study and therefore does not account for evidence from other endpoints from studies that may suggest potential impacts at lower dose levels (see discussion below on other candidate TRVs, including evidence from Gilman *et al.*, 1998, cited in CCME, 2007). The oral intubation exposure pathway in Paternain *et al.* (1989) is not as representative of environmental exposures as exposures through other oral pathways (e.g., diet or drinking water).

Evaluation of candidate TRVs

Table A.13. Candidate mammalian toxicity reference values (TRVs) for uranium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.49	CCME, 2007; Allaway and Stodola, 2011
0.615	CCME, 2007; Allaway and Stodola, 2011
6.13	**Sample *et al.*, 1996**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Although the selected TRV is the highest of the three TRVs available for evaluation, it was the only TRV based on relevant biological endpoints. The other two TRVs (0.49 and 0.615 mg/kg bm/day from CCME, 2007) were based on endpoints considered to be less relevant for FCSAP ("general deterioration of health" and renal effects) because it is difficult to relate them to population-level effects. The TRV from CCME (0.49 mg/kg bm/day), which was the daily effect threshold dose (DTED), was based on renal effects, which are the most sensitive indicator of uranium toxicity to mammals. Although renal damage can lead to increased mortality, it is unclear how well renal endpoints are quantitatively related to survival and therefore to population effects. CCME identified and discussed a total of 22 different mammalian uranium toxicity studies for a variety of species. However, CCME focused on toxicity data for rabbits orally exposed to uranium, because rabbits were considered a more ecologically relevant species than rats or other species. Ultimately, CCME (2007) selected only one study (Gilman *et al.*, 1998) to form the basis of its DTED. The other CCME TRV (0.615 mg/kg bm/day) is from the only available toxicity study for mammalian livestock (Garner, 1963) and represents a LOAEL for general health and milk yield of cows. This TRV on its own was not considered a suitable default TRV for FCSAP because it is focused on only one species (cow) and uses an endpoint (i.e., “general deterioration of health”) of uncertain relevance to protecting populations.

Although the two TRVs from CCME (2007) were not selected as default TRVs for FCSAP, they do provide important toxicological context and may still be considered on a site-specific basis, depending on site-specific receptors and other considerations. To give additional context to the selected default TRV (6.13 mg/kg bm/day; Sample *et al.*, 1996), the highest dose level tested in the Gilman *et al.* (1998) study on rabbits corresponded to 28.7 mg/kg bm/day and was associated with significant effects on kidney physiology and pathology. Gilman *et al.* considered that dose-level to be potentially lethal. The lowest reported chronic oral exposure NOAEL and LOAEL values for haematological and renal effects cited in CCME (2007) were 19 and 39 mg/kg bm/d, respectively, in rats exposed to uranyl nitrate hexahydrate for 2 years (Maynard *et al.* 1953). These toxicity data, along with other toxicity data cited in CCME (2007) but not directly included in the derivation of any of the presently available wildlife TRVs, help to provide some additional context for the selected FCSAP default uranium TRV.

Suggestions for improved future TRVs

There is potential to improve future mammalian TRVs for uranium. For example, there are a variety of toxicity data cited in CCME (2007) that are not directly incorporated into the development of any of the currently available TRVs. Future TRV derivations (either default or site-specific TRVs for sites where uranium is a concern) may benefit from further investigation of the toxicity data cited in existing TRV sources, a literature review of any potential additional and/or more recent toxicological data, and application of FCSAP-recommended TRV derivation methodology (FCSAP, 2010b), such as dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014). These potential future steps will help incorporate a greater depth of toxicological information into uranium effects and risk assessments.

Vanadium [Metal]

Receptor: Mammals

Selected TRV = 4.16 mg/kg bm/day
Source: USEPA, 2005e
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 101 results (48 studies) and is the highest bound NOAEL below the lowest bound LOAEL for reproduction, growth and survival endpoints. The study database includes information on five species (rat, mouse, rabbit, pig and sheep) and is therefore considered to be representative of all mammals. However, due to the NOAEL-based derivation methods, the selected TRV may be overly conservative for the FCSAP program.

Merits of the selected TRV

The TRV was derived using multiple studies (n=48) and multiple mammalian species (n=5) and is therefore a good reflection of the broad range of environmental exposure conditions and receptors (as opposed to a TRV derived from a single study). The study dataset included relevant biological endpoints and, for the most part, study conditions were representative of actual field conditions (study length > 250 days, exposure through diet, inorganic chemical forms of vanadium). No allometric scaling or uncertainty factors were applied.

Limitations of the recommended default TRV

The main limitation of this TRV is that it was derived using NOAEL-based methods (as opposed to dose-response), with only 15% of the NOAELs in the dataset being bound. Because the effect size for the selected TRV has not been quantified, there is a possibility that it is overly conservative for FCSAP objectives. However, in the USEPA dataset, effects were reported at values below the NOAEL-based TRV (4 of the 25 LOAELs for reproduction, growth and survival in the dataset are lower than the selected TRV).

Evaluation of candidate TRVs

Table A.14. Candidate mammalian toxicity reference values (TRVs) for vanadium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
2.1	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
4.16	**USEPA, 2005e; Allaway and Stodola, 2011; Dillon, 2013**
6	Rae, 2013
9.4	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four mammalian TRVs for vanadium, ranging from 2.1 mg/kg bm/day to 9.4 mg/kg bm/day, were evaluated. The lowest TRV (2.1 mg/kg bm/day; Sample *et al.*, 1996) was not selected, primarily because it is based on a single study and therefore has limited application to protect a variety of species, endpoints, and exposure conditions. This TRV is based on an unbound LOAEL for reproductive endpoints (number of dead young per litter, and size and weight of offspring), from a single rat study

(Domingo *et al.* 1986). Additionally, Domingo *et al.* (1986) did not use exposure pathways that are reflective of actual conditions in the field, as rats were exposed to vanadium for 60 days via oral intubation.

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (4.16 mg/kg bm/day; USEPA, 2005e), the geometric mean of reproductive, growth, and survival NOAELs (6 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (9.4 mg/kg bm/day). All three of these TRVs are based on multiple studies and are quite close together, especially relative to the whole range of NOAEL and LOAEL values in the USEPA dataset. For example, NOAELs for reproduction, growth, or survival range between 0.02 and 21695 mg/kg bm/day, and the LOAELs for those same endpoints range between 1.88 and 108 mg/kg bm/day. Note that the upper value in the range of NOAELs appears to be some kind of outlier; the next highest value in the USEPA (2005e) set of NOAELs for reproduction, growth, and survival is 136 mg/kg bm/day. Overall, all three of these TRVs fall within the lower end of the distribution across multiple studies and likely provide a similar level of protection. However, none of the three provide a quantitative measure of the level of effect that they represent. There is therefore no clear method for selecting the TRV that provides a level of protection most consistent with no more than minimal to low level of effects. The most conservative TRV (4.16 mg/kg bm/day; USEPA, 2005e) was thus selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

Given the wide range in values from the somewhat small amount of toxicological data available in the USEPA dataset, derivation of future TRVs would benefit from application of dose-response type methodology, as described in FCSAP (2010b), to maximize the utility of limited toxicology data. In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the available toxicological study(ies) and could also be tailored for site-specific purposes.

Zinc [Metal]

Receptor: Mammals

Selected TRV = 75.4 mg/kg bm/day
Source: USEPA, 2007e
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 99 studies and is the geometric mean of 69 NOAELs for relevant biological endpoints (growth and reproduction). The study dataset was based on multiple mammalian species (mouse, rat, sheep, pig, hamster and cattle) and is therefore considered to be representative of all mammals. Since the TRV was derived using NOAEL-based methods, it is considered to provide a level of protection consistent with a minimal to low level of effects, although it may be overly conservative.

Merits of the selected TRV

Derivation of the selected TRV considered many different toxicological studies (n=99) and a number of relevant biological endpoints to calculate a geometric mean. The TRV therefore captures a broad range of environmental exposure conditions and mammalian receptors. Studies were well designed to reflect conditions in the field because exposure durations were of sufficient length (up to 1 year) and exposure pathways were mostly dietary. No allometric scaling or uncertainty factors were applied.

Limitations of the recommended default TRV

The USEPA study uses a NOAEL-based approach to derive a zinc TRV for mammals. The effect size is uncertain, so there is a possibility that the TRV is overly conservative for FCSAP objectives. Additional uncertainties arise from the fact that the majority of the NOAELs and LOAELs in the USEPA dataset are unbound. Zinc is also an essential nutrient for mammals, with a strong relationship to calcium in the diet (CCME, 2018). Therefore, there may be a need on a site-specific basis to derive more receptor- and site-specific TRVs that account for zinc deficiency as well as toxicity, as well as the complex interactions with other essential nutrients.

Evaluation of candidate TRVs

Table A.15. Candidate mammalian toxicity reference values (TRVs) for zinc

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
9.6	USEPA Region 9 BTAG, 2009
20	OMOE, 2011; Allaway and Stodola, 2011; Dillon, 2013
75.4	**USEPA, 2007e; Dillon, 2013**
87	Rae, 2013
290	Rae, 2013
320	Sample *et al.*, 1996; OMOE, 2011; Allaway and Stodola, 2011
323.3	CEAEQ, 2012

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Seven TRVs, ranging from 9.6 mg/kg bm/day to 323 mg/kg bm/day, were evaluated. The two lowest TRVs (9.6 and 20 mg/kg bm/day respectively from USEPA Region 9 BTAG, 2009, and OMOE, 2011) were not selected as defaults for FCSAP because there was not enough information available about their derivation or underlying toxicological data to complete an evaluation. Furthermore, these two TRVs were derived from a single study and therefore have limited and uncertain application to a broad range of species, endpoints, or exposure conditions. Similarly, the LOAEL-based TRV of 320 mg/kg bm/day (Sample, *et al.*, 1996) was not considered appropriate as a default wildlife TRV for FCSAP because it is based on a single rat study with an unknown effect size, and it is therefore uncertain whether this TRV provides a sufficient level of protection consistent with a minimal to low level of effects. The TRV from CEAEQ (2012; 323.3 mg/kg bm/day) is also based on the same underlying toxicity data as the Sample *et al.* (1996; 320 mg/kg bm/day) TRV, except that it had allometric scaling applied to convert from rat to mouse-equivalent dose.

The remaining three TRVs are based on the USEPA dataset and represent the geometric mean of reproduction and growth NOAELs (75.4 mg/kg bm/day; USEPA, 2007e), the geometric mean of reproductive, growth, and survival NOAELs (87 mg/kg bm/day; Rae, 2013), and the geometric mean of reproductive, growth, and survival LOAELs (290 mg/kg bm/day; Rae, 2013). All three of these TRVs are based on multiple studies and all three are similar, particularly relative to the range of NOAEL and LOAEL values in the USEPA dataset. For example, reproductive, growth, and survival LOAELs (n=33) range from 8.71 to 4927 mg/kg bm/day (NOAELs for the same endpoints have a very similar range; 4.33 to 4878 mg/kg bm/day; n=86). However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that provides a level of protection most consistent with a minimal to low level of effects. Therefore, the most conservative of these three TRVs (75.4 mg/kg bm/day; USEPA, 2007e) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

Given the wide range in values for NOAELs and LOAELs in the USEPA toxicity dataset, derivation of future TRVs would benefit from application of dose-response type methodology, as described in FCSAP (2010b), to maximize the utility of available toxicology data. In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would help calculate a more quantitative level of protection for future default or site-specific TRVs.

Anthracene [LMW PAH]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable for FCSAP.

Table A.16. Candidate mammalian toxicity reference values (TRVs) for anthracene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
200	CCME, 2007; Allaway and Stodola, 2011; Dillon, 2013
1,000	OMOE, 2011; CCME, 2007

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

In general, very limited mammalian toxicity data are available for anthracene. Both of the TRVs considered by FCSAP are based on the same study (USEPA, 1989a), with an uncertainty factor of 5 applied to the 200 mg/kg bm/day TRV. USEPA (1989a) derived the TRV as an unbound NOAEL for survival and growth from an acute laboratory study on mice administered a daily dose of anthracene by gavage. The lack of underlying toxicity data is a major concern, and therefore neither TRV can be recommended for use as a default by FCSAP.

Suggestions for improved future TRVs
Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Fluorene [LMW PAH]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable for FCSAP.

Table A.17. Candidate mammalian toxicity reference values (TRVs) for fluorene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
50	CCME, 2010; Allaway and Stodola, 2011; Dillon, 2013
125	LANL, 2014

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Limited mammalian toxicity data are available for fluorene, and a single study (USEPA, 1989b) was used to derive both of the TRVs evaluated by FCSAP. Ultimately, no TRV was selected for fluorene because major concerns exist regarding the TRVs' limitations. The lower value (50 mg/kg bm/day) is the LOAEL for hematological effects from USEPA (1989b; 250 mg/kg bm/day), divided by an uncertainty factor of 5. The higher value (125 mg/kg bm/day; LANL, 2014) is the NOAEL for hematological effects from USEPA (1989b) with no uncertainty factors applied. There are several limitations associated with both TRVs, including use of NOAELs and LOAELs with unspecified effect size, the application of uncertainty factors, the applicability of mice data to all mammals, uncertain ecological relevance of the biological endpoints in USEPA (1989b; hematological effects include red blood cell count, packed cell volume, liver weight and hemoglobin), an experimental exposure pathway (via gavage) that is not reflective of relevant exposure pathways, and reliance on a single toxicological study. The degree of departure from FCSAP-recommended TRV derivation methodology led to the conclusion that no default TRV can be selected for FCSAP use at this time.

Suggestions for improved future TRVs
Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Supporting Scientific Rationale for FCSAP TRV Evaluation

Naphthalene [LMW PAH]

Receptor: Mammals

Selected TRV = 14.3 mg/kg bm/day
Source: LANL, 2014
Grade: B

Basis for the selected TRV

The selected TRV was derived by LANL (2014) as the geometric mean of nine chronic NOAELs for reproduction, development, growth, and survival endpoints, from toxicity studies with mice, rats, or rabbits. Some NOAELs included in the geometric mean were the result of application of uncertainty factors, while others were the result of dividing an unbound experimental LOAEL by a factor of 10. Chronic NOAELs were calculated either from acute NOAELs by dividing by a factor of 100 or from subchronic NOAELs by dividing by a factor of 10.

Merits of the selected TRV

The selected TRV was derived using NOAELs from multiple toxicological studies across a range of relevant endpoints (reproduction, growth, and survival), thereby reducing the TRV's reliance on a single toxicity study and possible outliers or tail ends of the natural distribution of responses associated with naphthalene exposure. No allometric scaling was applied to the underlying toxicity data.

Limitations of the recommended default TRV

This TRV is based on data for only rats, mice, and rabbits. Therefore, it is uncertain how well this TRV applies to other mammalian receptors. A mixture of exposure pathways were used in the underlying toxicity data. Some studies used oral exposure (e.g., through diet), which is preferred as a more relevant pathway, whereas other studies exposed animals via gavage, a less relevant pathway.

The use of uncertainty factors to calculate chronic NOAELs from LOAELs and/or acute or subchronic exposures is inconsistent with current FCSAP guidance (FCSAP, 2010b). It is also potentially misleading and may lead to an inappropriate level of protection at FCSAP sites (since it is not known whether the use of uncertainty factors leads to an overly or insufficiently conservative TRV). The implications of these uncertainty factors for a hazard assessment are further obscured by the use of a geometric mean across multiple studies, some of which use uncertainty factors, some of which do not. Therefore, there is uncertainty associated with the level of protection provided by this TRV.

Evaluation of candidate TRVs

Table A.18. Candidate mammalian toxicity reference values (TRVs) for naphthalene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
10	OMOE, 2011
14.3	**LANL, 2014**
28.6	CCME, 2010
50	USEPA Region 9 BTAG, 2009
150	USEPA Region 9 BTAG, 2009
295.44	Sanexen, 2002

Six TRVs for naphthalene, ranging from 10 to 295.44 mg/kg bm/day, were evaluated. For most of the candidate TRVs (four of six), there are several concerns and uncertainties associated with their derivation methods that preclude their selection as default values for FCSAP. Sources of concern include not providing a sufficient level of protection for a default TRV for FCSAP (OMOE, 2011), the use of gavage as an exposure pathway (CCME, 2010; LANL, 2014; USEPA Region 9 BTAG, 2009), underlying toxicity data limited to single studies (CCME, 2010; OMOE, 2011; Sanexen, 2002; USEPA, 2009), and the application of uncertainty factors and allometric scaling (CCME, 2010; LANL, 2014, OMOE, 2011, Sanexen, 2002). Although several of these concerns would not, on their own, necessarily be sufficient to preclude selection of these TRVs, it was the combination of several uncertainties that precluded their selection. Of the remaining two studies, the TRV of 28.6 mg/kg bm/day from CCME (2010) was based on a single rat study, whereas the TRV of 14.3 mg/kg bm/day (LANL, 2014) was based on a geometric mean of a variety of studies (n=9).

The USEPA TRV for LMW PAHs (65.6 mg/kg bm/day; USEPA, 2007d) was not considered as a candidate naphthalene TRV because it was intended to be applied to all LMW PAHs and included toxicity data for chemicals other than naphthalene.

Suggestions for improved future TRVs

There is room for improvement in future TRVs (either default or site-specific TRVs) through further investigation of the toxicity data cited in existing TRV and toxicity data sources, a literature review for any potential additional and/or more recent toxicological data, and application of FCSAP-recommended TRV derivation methodology (FCSAP, 2010b), such as dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014). This approach is likely to be especially valuable for improving TRVs that, like the selected default TRV, are based on a relatively small dataset and can therefore be more sensitive to outliers. These potential future steps will contribute to incorporating a greater depth of toxicological information into naphthalene effects and risk assessments and help quantify the level of protection provided by future TRVs.

Phenanthrene [LMW PAH]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable for FCSAP.

Table A.19. Candidate mammalian toxicity reference values (TRVs) for phenanthrene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
70	OMOE, 2011; Allaway and Stodola, 2011; Dillon, 2013
140	CCME, 2010

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Very limited mammalian toxicity data are available for phenanthrene. Therefore, only two TRVs were evaluated by FCSAP, both of which originate from the same study (Eisler, 1987). Eisler (1987) is an LD50 study in which rats were exposed to a single dose of phenanthrene at a concentration of 700 mg/kg bm. The discrepancy between the two TRV values stems from the uncertainty factor applied: an uncertainty factor of 10 was applied to derive a TRV of 70 mg/kg bm/day and an uncertainty factor of 5 was applied to derive a TRV of 140 mg/kg bm/day. The Eisler (1987) study is not consistent with FCSAP-recommended TRV derivation methods because it is based on a single study with unbound data, uses a single test species, and has not been demonstrated to provide an adequate level of protection for default FCSAP values. Moreover, the single dose of exposure is not reflective of actual environmental conditions. Therefore, a FCSAP TRV could not be not recommended at this time. Although not evaluated in this matrix, a TRV of 65.6 mg/kg bm/day is recommended by USEPA (2007d) for all LMW PAHs, which includes phenanthrene. However, as none of the underlying data used to derive the LMW PAH was based on phenanthrene, its applicability as a phenanthrene TRV is questionable at this time and merits further investigation.

Suggestions for improved future TRVs
Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-

evidence approach. The USEPA LWM PAH TRV of 65.6 mg/kg bm/day may also be assessed in detail to determine if it is appropriate for use as a phenanthrene TRV.

Low Molecular Weight Polycyclic Aromatic Hydrocarbons (LMW PAHs)

Receptor: Mammals

Selected TRV = 65.6 mg/kg bm/day
Source: USEPA, 2007d
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset (2007d) and is the highest bound NOAEL that is lower than the lowest bound LOAEL for reproduction, growth, and survival endpoints for low molecular weight (LMW) PAH toxicity data. The TRV was derived from a study by Verschuuren *et al.* (1976), reporting a growth endpoint for rats exposed to 1-naphthaleneacetic acid in food for 6 weeks. The USEPA dataset was generally limited to data for mice, rats, and rabbits typically exposed to LMW PAHs via gavage or occasionally through food. The majority of the toxicity data in the USEPA dataset was for naphthalene, with very limited data for other LMW-PAHs.

Merits of the selected TRV

The selected TRV was derived using NOAELs and LOAELs from multiple toxicological studies (30 NOAELs and 18 LOAELs for reproductive, growth, or survival endpoints). No allometric or uncertainty factors were used, and the study design is generally reflective of actual conditions.

Limitations of the recommended default TRV

The selected TRV is potentially overly conservative because it is based on a NOAEL at the lower end of the distribution of all reproductive, growth, and survival endpoints in the USEPA dataset. There are only two values for those three endpoints in the USEPA dataset that are below the selected TRV (an unbound NOAEL for survival, and an unbound LOAEL for growth; both 50 mg/kg bm/day). Other potential limitations associated with this TRV include the abundance of toxicity data based on gavage exposure, which is not representative of typical exposure pathways in the environment, the limited set of species, and dominance of a single LMW PAH (naphthalene) represented in the toxicity dataset.

Evaluation of candidate TRVs

Table A.20. Candidate mammalian toxicity reference values (TRVs) for LMW PAHs

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
65.6	**USEPA, 2007d**

The selected TRV has its limitations (described above). However, it was the only TRV available for application to LMW PAHs (as a sum of individual LMW PAHs). This selected TRV may be used as default value for FCSAP.

Suggestions for improved future TRVs

There is room for improvement in future TRVs (either default or site-specific TRVs) through further investigation of the toxicity data cited in existing TRV sources, a literature review for any potential additional and/or more recent toxicological data, and application of FCSAP-recommended TRV derivation methodology (FCSAP, 2010b), such as dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014). This approach is likely to be especially valuable for

improving TRVs that, like the selected default TRV, are based on a relatively small dataset and can therefore be more sensitive to outliers. These potential future steps will contribute to incorporating a greater depth of toxicological information into LMW-PAH effects and risk assessments and will help improve quantification of the level of protection provided by future TRVs.

Benzo(a)anthracene [HMW PAH]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable as default values for FCSAP.

Table A.21. Candidate mammalian toxicity reference values (TRVs) for benzo(a)anthracene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.167	USEPA, 1999
0.17	LANL, 2014
20	CCME, 2010; Allaway and Stodola, 2011; Dillon, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

No mammalian benzo(a)anthracene TRV could be selected for use as a default by FCSAP at this time because of substantial limitations and deviations from FCSAP guidance for TRV derivation. All three TRVs were derived using LOAEL or NOAEL data from only one study each. None of the three studies used acceptable biological endpoints (survival, growth and reproduction). USEPA (1999), LANL (2014), and CCME (2010) TRVs were based on gastrointestinal, tumour growth, and immunosuppression endpoints in mice, respectively, all of which are difficult to extrapolate to population-level effects in other mammal species. All three TRVs applied uncertainty factors to approximate a chronic TRV from toxicity experiments that applied a single one-time dose of benzo(a)anthracene. CCME (2010) divided the dose by an uncertainty factor of 5, and LANL (2014) and USEPA (1999) both divided the dose by an uncertainty factor of 10 to compensate for the short exposure duration in the underlying toxicity test. There is no quantification of effect size available for any of these TRVs, making it difficult to evaluate the level of protection they provide.

Suggestions for improved future TRVs
Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include other lines of evidence to inform effects assessments within a broader weight-of-evidence approach. A search for any additional toxicity data and application of dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014) and currently

recommended TRV development methodology (FCSAP, 2010b) will potentially improve the level of confidence associated with values used to assess risk to mammals from benzo(a)anthracene. Also, because additional toxicity data may be scarce, other lines of evidence may be incorporated into future TRV development to relate the endpoints behind current TRVs (e.g., immunosuppression) to potential population-level effects.

Benzo(a)pyrene [HMW PAH]

Receptor: Mammals

Selected TRV = 3.6 mg/kg bm/day
Source: CEAEQ, 2012
Grade: C

Basis for the selected TRV

The selected TRV is from CEAEQ (2012) and was derived from a single study, Mackenzie and Angevine (1981), which exposed mice to three experimental dose levels (10, 40, and 160 mg/kg bm/day) of benzo(a)pyrene in their diet. This TRV represents an EC_{20} for reproductive capacity calculated from the toxicity data (the lowest tested dose of 10 mg/kg was associated with 60% reduction in reproductive capacity of test animals).

Merits of the selected TRV

Mackenzie and Angevine (1981) exposed mice to benzo(a)pyrene through their diets, which is considered a relevant exposure pathway. The assessment endpoint was reproduction, which represents an acceptable biological endpoint that can be applied to population-level effects. There is a quantitative effect level (20%) associated with this TRV, which confers that this TRV is supportive of intended level of protection for default wildlife TRVs for FCSAP (i.e., no more than minimal to low level of effects to common species). Finally, no uncertainty factors were used in the derivation of this TRV.

Limitations of the recommended default TRV

The selected TRV for benzo(a)pyrene is derived from a single study and extrapolated to an effect level (20%) below the lowest tested experimental dose level (60% reproductive effect at the 10 mg/kg bm/day experimental dose level) for a single species (mouse), which means that its application and extrapolation to a broader set of exposure conditions, other dose levels, and other mammalian species is uncertain. This TRV also applied a minor allometric scaling to convert from a 20-gram mouse (the weight reported for experimental animals), to a 21-gram mouse equivalent (the standard mouse-weight selected by CEAEQ, 2012, for their TRV derivation methodology). Application of allometric scaling is not consistent with current preferred methodology for TRV development (FCSAP, 2010b), but in this case the implications are minimal.

Evaluation of candidate TRVs

Table A.22. Candidate mammalian toxicity reference values (TRVs) for benzo(a)pyrene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.1	USEPA, 1999
1	Sample *et al.*, 1996; Williams *et al.*, 2015
1.31	USEPA Region 9 BTAG, 2009
2	CCME, 2010
3.6	**CEAEQ, 2012**
5.58	LANL, 2014
10	Sample *et al.*, 1996; Allaway and Stodola, 2011; Dillon, 2013; Williams *et al.*, 2015
32.8	USEPA Region 9 BTAG, 2009
40	OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

A total of nine mammalian TRVs for benzo(a)pyrene, ranging from 0.1 to 40 mg/kg bm/day, were evaluated. Some of the TRVs were screened out because of insufficient information in the primary literature to properly assess derivation methods (1.31 and 32.8 mg/kg bm/day; USEPA Region 9 BTAG, 2009). Five of the TRVs (0.1, 1, 2, 10 and 40 mg/kg bm/day) were screened out because the associated effect size was potentially not conservative enough to provide a level of protection consistent with a minimal to low level of effects. All five were based on the same single toxicity study (Mackenzie and Angevine, 1981). There is a 60% effect size associated with the 10 mg/kg bm/day dose level (a reproductive LOAEL without any uncertainty factors applied) and a 97% effect on sterility at the 40 mg/kg bm/day dose level, both of which are too severe to protect from no more than minimal to low level of effects. There is no supporting quantitative scientific rationale that the uncertainty factors applied to the 10 mg/kg bm/day LOAEL dose level from Mackenzie and Angevine (1981) to derive the 0.1, 1, and 2 mg/kg bm/day TRVs (USEPA, 1999; Sample *et al.*, 1996; and CCME, 2010, respectively) would result in an acceptable effect level with a minimal to low level of effects to common species. The TRV from CEAEQ (2012; 3.6 mg/kg bm/day) was also based on the Mackenzie and Angevine (1981) study, but rather than the application of uncertainty factors, an EC_{20} for the reproductive endpoint was calculated from the toxicity data.

The TRV from LANL (2014) was the only available TRV that considered multiple toxicity studies (rat and mouse) and therefore integrates toxicity data across a range of exposure conditions and pathways (both via gavage and via diet), as is relevant for a default wildlife TRV for FCSAP. Although the effect level associated with this TRV is not explicitly quantified, it is likely to provide an appropriate level of protection for FCSAP default TRVs because it was based on a geometric mean of 13 chronic NOAELs for reproduction, development, growth, and survival endpoints, from 10 studies on rat toxicity (including the 1981 Mackenzie and Angevine , toxicity study, on which six of the other candidate TRVs are based). Some NOAELs included in the geometric mean had uncertainty factors applied, and some NOAELs were the result of dividing an unbound experimental LOAEL by a factor of 10. Chronic NOAELs were calculated from either acute NOAELs, by dividing by a factor of 100, or from subchronic NOAELs, by dividing by a factor of 10.

The USEPA (2007d) TRV for HMW PAHs (0.615 mg/kg bm/day) was not evaluated as a candidate mammalian TRV for benzo(a)pyrene because it was developed for a class of TRVs and included toxicity data for chemicals other than just benzo(a)pyrene. However, it helps provide additional context for evaluating toxicity of benzo(a)pyrene in risk assessments. For example, in the USEPA TRV derivation, no uncertainty factors were applied.A variety of test species, such as shrew and guinea pig, were considered in addition to rats and mice, and multiple relevant biological endpoints were incorporated (reproduction, growth, and survival). In addition, 59% of the underlying data used to derive the USEPA HMW PAH TRV were for benzo(a)pyrene. Applying USEPA TRV derivation methods to just this subset of toxicity data for benzo(a)pyrene still results in a TRV of 0.615 mg/kg bm/day.

Suggestions for improved future TRVs

There is room for improvement in future TRVs (either default or site-specific TRVs) through further investigation of the toxicity data cited in existing TRV sources, a literature review for any potential additional and/or more recent toxicological data, and application of FCSAP-recommended TRV derivation methodology (2010b), such as dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014). This approach is likely to be especially valuable for improving TRVs that, like the selected default TRV, are based on a relatively small dataset and can therefore be more sensitive to outliers. These potential future steps will contribute to incorporating a greater depth of toxicological information into benzo(a)pyrene effects and risk assessments and will help improve quantification of the level of protection provided by future TRVs.

Pyrene [HMW PAH]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable as default values for FCSAP.

Table A.23. Candidate mammalian toxicity reference values (TRVs) for pyrene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
25	CCME, 2010; Allaway and Stodola, 2011; Dillon, 2013
125	OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Limited mammalian toxicity data exists for pyrene, and the two TRVs that were evaluated by FCSAP both originate from the same study (USEPA, 1989c). Derivation methods for both TRVs are the same, except for an uncertainty factor of 5 being applied to 125 mg/kg bm/day to derive a TRV of 25 mg/kg bm/day. Overall, the confidence in these TRVs is low because they are based on a LOAEL value from a single mice study in which doses of 0. 75, 125 and 250 mg/kg bm/day were administered to mice by gavage. Measured endpoints were nephropathy and decreased kidney weight, which are not relevant biological endpoints that can be easily extrapolated to population-level effects. Therefore, a default or default value for FCSAP could not be recommended at this time. Although not evaluated in this matrix, a TRV of 0.615 mg/kg bm/day is recommended by USEPA (2007d) for all HMW PAHs (including pyrene). However, FCSAP questions its applicability to pyrene because none of the underlying toxicity data used to derive the HMW PAH TRV included mammalian toxicity data for pyrene.

Suggestions for improved future TRVs
Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

High Molecular Weight Polycyclic Aromatic Hydrocarbons [HMW PAHs]

Receptor: Mammals

Selected TRV = 0.615 mg/kg bm/day
Source: USEPA, 2007d
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset (2007d) and is the highest bound NOAEL that is lower than the lowest bound LOAEL for high molecular weight (HMW) PAH data. The result was the selection of a benzo(a)pyrene TRV from Culp *et al.* (1998). The USEPA dataset included data for four species of mammal (mouse, rat, shrew, and guinea pig) using relevant biological endpoints (reproduction, growth and survival) and a variety of different single HMW PAH chemicals.

Merits of the selected TRV

The selected TRV was derived using NOAEL/LOAEL from multiple toxicological studies across a range of mammalian species. No allometric or uncertainty factors were used, and the study design is generally reflective of actual conditions. For example, Culp *et al.* (1998) exposed test animals to benzo(a)pyrene through their diet and measured survival over a period of 55 weeks (chronic exposure duration).

Limitations of the recommended default TRV

USEPA's TRV is a NOAEL from Culp *et al.* (1998; 0.615 mg/kg bm/day). The selected TRV is potentially overly conservative because it is based predominately on NOAELs and is the lowest of the 32 NOAELs and LOAELs for reproduction, growth or survival included in USEPA dataset. Additionally, because the USEPA dataset only includes data for four types of mammals, it may not be representative of all mammals.

Evaluation of candidate TRVs

Table A.24. Candidate mammalian toxicity reference values (TRVs) for HMW PAHs

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
0.10	USEPA, 1999
0.615	**USEPA, 2007d**

Two TRVs for HMW PAHs were evaluated. The TRV from USEPA (1999; 0.10 mg/kg bm/day) used toxicity data from one study (Mackenzie and Angevine, 1981), and applied benzo(a)pyrene as a surrogate to represent all HMW PAHs. In addition, that TRV applied an uncertainty factor of 0.01 to estimate a chronic NOAEL for reproductive effects from an unbound LOAEL. The USEPA (2007d) TRV considers a much greater variety of toxicity data, for a variety of different HMW PAHs, species, and endpoints. Also, USEPA (2007d) developed that TRV with the explicit intention of recommending a single TRV to represent all HMW PAHs (as a sum of individual HMW PAHs).

Suggestions for improved future TRVs

There is room for improvement in future TRVs (either default or site-specific TRVs) through further investigation of the toxicity data cited in existing TRV sources, a literature review for any potential additional and/or more recent toxicological data, and application of FCSAP-recommended TRV

derivation methodology (2010b), such as dose-response methodology (e.g., recommendations for sparse datasets described in Hill *et al.*, 2014). This approach is likely to be especially valuable for improving TRVs that, like the selected default TRV, are based on a relatively small dataset and can therefore be more sensitive to outliers. These potential future steps will contribute to incorporating a greater depth of toxicological information into HMW-PAH effects and risk assessments and will help improve quantification of the level of protection provided by future TRVs.

Benzene [Volatile Organic]

Receptor: Mammals

Selected TRV = 2.62 mg/kg bm/day
Source: Sanexen, 2002
Grade: B

Basis for the selected TRV

The selected default value is derived from Sanexen (2002) using Weibull statistical methods to establish a dose-response curve from 11 benzene toxicity studies. Test species included rats and mice; all mammalian data were then converted to 21-gram mouse-equivalent data using allometric scaling so that the 20% effect level for each study could be identified. Finally, the lowest EC_{20} value for all 11 studies was selected by Sanexen (2002) as their recommended TRV.

Merits of the selected TRV

The selected TRV was derived from multiple toxicity studies (n=11) and applied dose-response methods, which allow for the selection of a TRV value at a 20% effect level. Other merits include the use of relevant biological endpoints (reproduction, growth and survival), which can be easily extrapolated to population-level effects.

Limitations of the recommended default TRV

Although the selected TRV utilized a dose-response curve, not all facets of the derivation methodology were in line with FCSAP recommendations. For example, allometric scaling was used to convert all mammalian data to 21-gram mouse-equivalent data, and uncertainty factors were applied to account for the acute nature of some of the toxicity studies. Also, gavage was used as an exposure pathway in some studies, which is not reflective of exposure pathways in the natural environment. Lastly, because only two species of mammals are represented in the underlying toxicity data, the TRV may not be applicable to all mammals.

Evaluation of candidate TRVs

Table A.25. Candidate mammalian toxicity reference values (TRVs) for benzene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.08	Environment Canada, 2005a
2.62	**Sanexen, 2002**
8.97	Sanexen, 2002
264	Sample *et al.*, 1996; Allaway and Stodola, 2011; LANL, 2014; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four TRVs with a wide range of values (0.08 to 264 mg/kg bm/day) were evaluated by FCSAP. Three TRVs were screened out either because they did not provide a sufficient level of protection (8.97 mg/kg bm/day, an EC_{40}) or because it was unclear whether certain LOAEL-based TRVs were sufficiently protective to be a default TRV for FCSAP (0.08 and 264 mg/kg bm/day). Further research could be conducted to quantify the effect sizes of the LOAEL values. However, these TRVs are also limited by

reliance on a single toxicity study and test species, unbound data, and in one case, the use of uncertainty factors and unacceptable biological endpoints. Therefore, the Sanexen (2002) TRV of 2.62 mg/kg bm/day was selected for use as a default value for FCSAP.

Suggestions for improved future TRVs

Updated literature searches for additional toxicology data may help supplement the currently limited set of available data. In addition, further investigation into the available toxicological data underlying the Sanexen (2002) TRV and application of recommended methodology from FCSAP (2010b) could quantitatively integrate and enhance the utility of limited toxicity data, leading to improved TRVs in the future.

Supporting Scientific Rationale for FCSAP TRV Evaluation

Ethylbenzene [Volatile Organic]

Receptor: Mammals

Selected TRV = 0.7 mg/kg bm/day
Source: Sanexen, 2002
Grade: C

Basis for the selected TRV

The selected TRV was derived by Sanexen (2002), which calculated an EC_{20} for each of five different studies reporting survival or kidney and liver lesion endpoints for rats or mice. Uncertainty factors were applied to the calculated EC_{20}s to account for toxicity tests of short exposure durations and for mortality endpoints. EC_{20}s were divided by an uncertainty factor of 2 for studies considered to have short test durations and also by an uncertainty factor of 5 if the study was based on a survival endpoint. Therefore, 10 was the highest total uncertainty factor applied to any one study in the Sanexen (2002) dataset. The selected TRV is the lowest of the five EC_{20}s evaluated by Sanexen (2002).

Merits of the selected TRV

Sanexen (2002) quantified the effect level at 20% for the underlying toxicity data, and it can therefore be confirmed that this TRV is based on a study that provides a level of protection consistent with a minimal to low level of effects. Multiple toxicity studies (n=5) were used in the TRV derivation, although four of these studies were rated as "low confidence" by Sanexen (2002). Users may refer to Sanexen for details on how it categorized confidence in individual studies. Other merits include inclusion of data for appropriate biological endpoints (survival) and the fact that ingestion is the exposure pathway.

Limitations of the recommended default TRV

The selected TRV was derived from data for a limited number of mammalian species (only mice and rats), which may not be protective of a broader range of mammals. The application of an uncertainty factor (of 2) to account for acute exposure duration and the mortality endpoints in the underlying toxicity tests add some uncertainty to the derivation process, as the implications of these for the level of protection provided by this TRV are unknown. Two of the studies in this dataset tested exposure via inhalation pathway, which is not as relevant as other exposure pathways (e.g., oral) to default wildlife TRVs for FCSAP. Furthermore, Sanexen (2002) gave four of the five studies included in its dataset a "low level of confidence," which means caution is warranted when applying this selected TRV (hence, the assignment of a C-grade).

Evaluation of candidate TRVs

Table A.26. Candidate mammalian toxicity reference values (TRVs) for ethylbenzene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.7	**Sanexen, 2002**
0.8	Sanexen, 2002
2.91	CCME, 2004
291	Allaway and Stodola, 2011; Dillon, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four TRVs, ranging from 0.7 to 291 mg/kg bm/day, were evaluated. The two highest TRVs (291 and 2.91 mg/kg bm/day) were both based on the same single toxicological study reporting a bound LOAEL for histopathological endpoints in kidney and liver from a single toxicological study by Wolf *et al.* (1956) that exposed rats to ethylbenzene via gavage for 182 days. The LOAEL from Wolf *et al.* (1956; 408 mg/kg bm/day) was multiplied by 5/7 to correct for exposure on 5 out every 7 days in the experiment. It was not possible to calculate an effect size associated with the LOAEL behind the TRV of 291 mg/kg bm/day. Therefore, if this TRV were to be applied in an ecological risk assessment, there is potential that it may not be sufficiently protective of mammalian receptors of concern on the site (i.e., LOAELs may be associated with a greater than 25% effect size). The TRV from CCME (2004, 2.91 mg/kg bm/day) is its daily threshold effect dose (DTED) and was derived by dividing the LOAEL from Wolf *et al.* (1956) by an uncertainty factor of 100. Therefore, both of these TRVs (2.91 and 291 mg/kg bm/day) were limited by their LOAEL-based derivation methods, gavage exposure pathway, and biological endpoints (liver and kidney weight), and their application to population-level effects to common species is uncertain.

The two TRVs from Sanexen (2002) were derived using the same dose-response type of methodology, the only difference being that the 0.7 mg/kg bm/day TRV correlates to an EC_{20} and the 0.8 mg/kg bm/day TRV correlates to an EC_{40}. The EC_{40} does not provide a level of protection likely to be consistent with no more than minimal to low level of effects. Therefore, it was not suitable as a default TRV for FCSAP.

Suggestions for improved future TRVs

To improve future effects assessments, updated literature searches for additional toxicology data may help supplement the currently limited set of available data so as to be able to put these TRVs into a broader context for multiple species, endpoints, and ecologically relevant exposure conditions. Future TRV development would also benefit from application of FCSAP-recommended TRV derivation methodology (FCSAP, 2010b). Other types of information (e.g., tissue residue- data) may also be investigated to further supplement and improve risk assessments within a weight-of-evidence approach.

Supporting Scientific Rationale for FCSAP TRV Evaluation

Toluene [Volatile Organic]

Receptor: Mammals

Selected TRV = 26 mg/kg bm/day
Source: Sample *et al.*, 1996
Grade: C

Basis for the selected TRV

The selected TRV is from Sample *et al.* (1996) and is based on a NOAEL calculated from an unbound LOAEL for a reproductive endpoint (embryonic lethality) for one species (mouse) from one study (Narwot and Staples, 1979). Test animals were exposed via gavage for 10 days during gestation.

Merits of the selected TRV

The selected TRV is based on an appropriate biological endpoint (embryonic lethality) that is relevant to population level dynamics. Allometric scaling was not used in the development of this TRV, which is consistent with FCSAP methodology (2010b).

Limitations of the recommended default TRV

The selected TRV is based on a single study for a single reproductive endpoint and a single species; it therefore has limited and uncertain relevance to wide range of environmental exposure scenarios occurring at federal contaminated sites. In addition, the magnitude of effect associated with the LOAEL behind this TRV is unknown and cannot be calculated at this time because of the limited availability of information relating to the underlying toxicological study. Only the abstract for Nawrot and Staples (1979) was available, and it did not contain enough information to quantify the level of effect associated with this TRV. The abstract for Nawrot and Staples (1979) reported "significant increase in embryonic lethality occurring at all dose levels." The unbound LOAEL from Nawrot and Staples (1979) was the lowest tested dose of 0.3 mL toluene/kg bm/day. It is thus difficult to quantify the level of protection provided by this TRV. An uncertainty factor of 10 was applied to approximate a NOAEL from a LOAEL.

Evaluation of candidate TRVs

Table A.27. Candidate mammalian toxicity reference values (TRVs) for toluene

Candidate TRV (mg/kg bm/day)	**Source (See Reference Section 3)[1]**
0.5	Sanexen, 2002
4.46	Environment Canada, 2005b
26	**Sample *et al.*, 1996; LANL, 2014**
260	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four mammalian TRVs for toluene were evaluated. The lowest TRV (0.5 mg/kg bm/day from Sanexen, 2002) was based on an EC_{20} calculated from one rat study selected by Sanexen (2002) through an evaluation of a set of six toxicological studies. The endpoint behind that TRV was not clearly defined

and therefore has uncertain relevance as a FCSAP default TRV. The TRV from Environment Canada (2005b; 4.6 mg/kg bm/day) was also based on endpoints with uncertain relevance for FCSAP defaults (i.e., histopathological changes in kidney and liver). The remaining two TRVs (26 and 260 mg/kg bm/day) were both based on the same underlying toxicological study, i.e., Narwot and Staples (1979). The higher TRV developed by Sample *et al.* (1996; 260 mg/kg bm/day) was not selected as a default for FCSAP because of the unknown effect size associated with the underlying LOAEL, which could potentially be too severe to provide the level of protection targeted for default wildlife TRVs for FCSAP.

Suggestions for improved future TRVs

To improve future effects assessments, updated literature searches for additional toxicology data may help supplement the currently limited set of available data so as to be able to put these TRVs into a broader context for multiple species, endpoints, and ecologically relevant exposure conditions. Future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b). Other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve risk assessments within a weight-of-evidence approach.

Supporting Scientific Rationale for FCSAP TRV Evaluation

Xylenes [Volatile Organic]

Receptor: Mammals

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable as default values for FCSAP.

Table A.28. Candidate mammalian toxicity reference values (TRVs) for xylenes

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
2.3	CEAEQ, 2012
11.9	AEP, 2016
500	OMOE, 2011; Allaway and Stodola, 2011
2100	Sample *et al.*, 1996 (originally reported incorrectly as 2.1 mg/kg bm/day); LANL, 2014

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Four TRVs, spanning a broad range from 2.3 to 2100 mg/kg bm/day, were evaluated. However, none were considered appropriate as default values for FCSAP. All available candidate TRVs represent potentially useful information for deriving new TRVs in the future, but none of these TRVs based on a single toxicological study could be considered suitable as a default value for FCSAP.

The middle two values (11.9 mg/kg bm/day from AEP, 2016, and 500 mg/kg bm/day from OMOE, 2011) were both based on the same rat growth LOAEL-endpoint from the same toxicity study (NTP, 1986). The only difference between these two numbers was that the AEP (2016) TRV (11.9 mg/kg bm/day) applied an uncertainty factor (division by 30) and a correction to account for the exposure frequency of 5 out of 7 days in the NTP (1986) toxicity test. The OMOE (2011) TRV (500 mg/kg bm/day) represents the nominal, unadjusted exposure dose in NTP (1986). Neither of these TRVs were selected because they were based on toxicity data for a mixture of chemicals (60% m-xylene, 14% p-xylene, 9% o-xylene, and 17% ethylbenzene). Therefore, the implications of applying these TRVs to evaluating risk from xylenes only are uncertain. These TRVs also had additional limitations, including the fact that they were based on a single study on a single species (rats), albeit for an ecologically relevant 2-year study

duration. The lowest TRV (2.3 mg/kg bm/day; CEAEQ, 2012) was not selected because it was derived from incorrectly reported toxicity data (i.e., off by a factor of 1000). The highest TRV (2100 mg/kg bm/day; LANL, 2014, and Sample *et al.*, 1996) was based on the same toxicity study as the CEAEQ (2012) TRV and has the limitation of being based on a single study that exposed rats via gavage. The underlying toxicity data was reviewed to determine that this TRV (2100 mg/kg bm/day) is based on a bound LOAEL associated with 12.3% reduced fetal growth (95% confidence interval of 9.7% to 18.1%), as well as significant increased incidence (by 3.4%) of fetal malformations, which would be considered an acceptable level of effect for a default TRV for FCSAP. However, given the broad, three orders of magnitude range across the available candidate TRVs, the lack of available analysis to understand this wide range in values, and the various limitations identified for individual TRVs (including limited data availability), there is not enough information available at this time to recommend a default TRV that is sufficient as a FCSAP default value that is demonstrated to be sufficiently protective and representative of a wide variety of exposure conditions or mammalian species.

Suggestions for improved future TRVs

Given the high degree of uncertainty and limitations associated with the available TRVs and the overall limited amount of toxicological data for mammalian xylene toxicity, there is room for improvement of future TRVs (either default or site-specific values). Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach. Future steps may help resolve the wide discrepancies between existing toxicity data and TRVs.

Petroleum Hydrocarbons [PHCs]

Receptor: Mammals

Selected TRV = 210 mg/kg bm/day (Total PHCs);
= 48.72 mg/kg bm/day (F1)
= 44.73 mg/kg bm/day (F2)
= 72.45 mg/kg bm/day (F3)
= 38.22 mg/kg bm/day (F4)
Source: AEP, 2016; CCME, 2008
Grade: C

Basis for the selected TRV

The selected TRV is from the CCME Canada-Wide Standard for Petroleum Hydrocarbons in Soil (CCME, 2008), which cites a threshold dose for effects in cattle from Stober (1962; as cited in Coppock and Campbell, 1997). The original toxicological study (Stober, 1962) was reviewed and revealed that this threshold dose was based on an unbound LOAEL for behavioural, blood chemistry, and liver functioning endpoints in cattle exposed to crude oil via food. All of these endpoints were found to be reversible within 8 to 10 days following exposure in the underlying toxicological study.

Merits of the selected TRV

There are many complexities and uncertainties associated with evaluating toxicity of PHCs which exist as complex mixtures of many different chemicals. This TRV represents recent extensive review of PHC toxicity by CCME (2008), which took into consideration many of the complexities associated with PHCs. The underlying toxicological study exposed cows to PHCs in a way that is likely very similar to how cows would be exposed to PHCs in environmental situations. Cows were exposed to PHCs through food contaminated with crude oil product. No allometric scaling or uncertainty factors were used, which is consistent methodology with FCSAP (2010b).

Limitations of the recommended default TRV

The selected TRV is based on potentially overly conservative endpoints that were also observed to be reversible in the underlying toxicological study. This TRV was based on a single study, with very small sample size (one cow in the treatment level that this TRV is based on). Therefore, it is not possible to quantify the magnitude of effect associated with this TRV. It is also not possible to quantify uncertainty associated with this TRV, in terms of natural range in biological responses to PHC exposure between different cows, or between different types of mammals. Additionally, Stober (1962) could not determine if the observed endpoints were necessarily due to toxicity through PHC exposure, or from malnutrition; given the option, cows would choose non-contaminated food over contaminated food, and cows with access to only contaminated food would choose not to eat. Therefore, this experimental design introduces uncertainty regarding the amount of chemical to which test animals were actually exposed. There is also uncertainty in terms of how well this TRV may apply to different types of PHCs with varying compositions; lighter PHC mixtures are typically considered more toxic than heavier PHC mixtures.

Evaluation of candidate TRVs

Table A.29. Candidate mammalian toxicity reference values (TRVs) for petroleum hydrocarbons (PHCs)

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
Whole PHC Product (e.g., crude oil)	
90	CCME, 2008
210	**CCME, 2008; AEP, 2016**
PHC Sub-Fractions	
F1: 48.72	**AEP, 2016; CCME, 2008**
F2: 44.73	**AEP, 2016; CCME, 2008**
F3: 72.45	**AEP, 2016; CCME, 2008**
F4: 38.22	**AEP, 2016; CCME, 2008**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

All candidate TRVs (Table A.29) for either whole PHC product or individual PHC sub-fractions are based on the same single underlying toxicity study with cattle (Stober, 1962), as cited in Canadian Council of Ministers of the Environment (CCME) Canada-Wide Standard (CWS) for Petroleum Hydrocarbons in Soil (CCME, 2008). Alberta Environment (AEP, 2016) used the daily threshold effect dose (DTED) of 210 mg/kg bm/day (from Stober, 1962 data; cited in CCME, 2008) to calculate fraction-specific water quality guidelines for wildlife and for livestock watering. AEP (2016) used the fractional composition of total petroleum hydrocarbons as presented in CCME (2008): F1 = 23.2% of total PHC mixture; F2 = 21.3% of total PHC mixture; F3 = 34.5% of total PHC mixture; and F4 = 18.2% of total PHC mixture.

TRVs for petroleum hydrocarbons are difficult to derive because PHCs exist as complex mixtures in the environment. PHCs vary widely in their chemical composition depending on their source and degree of environmental degradation. Therefore, the toxicity of PHCs can appear to vary between mixtures of different chemical compositions. There are various types of approaches for assessing the toxicity of PHCs. The TRVs considered in this module used data from toxicity tests on PHC mixtures (e.g., crude oil product). Additional information about PHC toxicity was also cited in CCME (2008, Appendix I), and threshold doses reported for PHCs ranged from 1100 mg/kg bm to 7300 mg/kg bm, based on toxicity studies using various different petroleum hydrocarbon products (i.e., un-weathered or weathered crude oil, Venezuela crude oil, or Bunker “C” oil).

Another approach to risk assessment of PHC mixtures is to apply data on the toxicity of individual surrogate chemicals to represent the toxicity of mixtures. This method using surrogate chemicals assumes similar and additive toxicity of all PHC components within the mixture. For example, the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG) published a comprehensive review of PHC toxicity (Edwards *et al.*, 1997) and applied a surrogate approach to assessing effects from PHCs. The values presented by the TPHCWG (Edwards *et al.*, 1997) were developed with a focus on protection of human health and therefore were not considered as candidate TRVs for protection of wildlife in this module. However, the derivation of these values included toxicity data for rats and mice, which would be relevant to derivation of TRVs for protection of other mammals. Therefore, the information in Edwards *et al.* (1997) may help inform future TRV derivation.

Suggestions for improved future TRVs

To improve future effects assessments, updated literature searches for additional toxicology data may help supplement the currently limited set of available data so as to be able to put these TRVs into a broader context for multiple species, endpoints, and ecologically relevant exposure conditions. In addition, future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) to existing PHC toxicological data. Other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve risk assessments within a weight-of-evidence approach.

Polychlorinated Biphenyls [PCBs]

Receptor: Mammals

Selected TRV = 0.19 ng TEQ/kg bm/day
Source: CCME, 2001a
Grade: C

Basis for the selected TRV

This TRV is also the basis for the current Canadian Tissue Residue Guideline for the Protection of Wildlife Consumers of Aquatic Biota (CCME, 2001a). Complete details on the derivation of this value are provided in CCME (2001a). It should be noted that the TRV for PCBs is expressed in **units of ng toxic equivalency units (TEQs)/kg bm/day**. This TRV is based on the geometric mean of the NOAEL and LOAEL for second generation juvenile mink growth in a toxicological study by Wren *et al.* (1987). An uncertainty factor of 10 was applied to the geometric mean of the NOAEL and LOAEL to accommodate differences in interspecies sensitivities to PCBs. The study by Wren *et al.* (1987) was selected as the basis for the CCME (2001a) tissue residue guideline because it had the lowest reference concentration for mammalian species across a range of different species and studies.

Merits of the selected TRV

The toxicological study was selected from a set of studies that included a range of species (mink, rats, monkeys, pigs, and ferrets) and is therefore likely to be protective of a range of mammalian species on federal contaminated sites. This TRV is also based on a relevant reproductive endpoint (growth of kits from adult mink exposed to PCBs). As a unique issue to PCB TRVs, this value applied toxic equivalency factors (TEFs), as recommended by the World Health Organization (van den Berg *et al.*, 1998), so that toxicities of PCB mixtures with different PCB congener compositions could be directly compared (see CCME 2001a for a description of TEFs and how they were applied in deriving this TRV).

Limitations of the recommended default TRV

The magnitude of effect associated with this TRV is not quantified because the TRV was derived as the geometric mean of a NOAEL and LOAEL value and divided by an uncertainty factor of 10 to account for interspecies sensitivities to PCBs. The LOAEL used in the geometric mean behind this selected TRV was associated with a 25% to 30% reduction in mink kit growth, which on its own is too severe for a FCSAP default TRV to provide a level of protection consistent with no more than minimal to low level of effects. The NOAEL that was used in the geometric mean behind this TRV was calculated as the LOAEL divided by 5.6. Therefore, there is uncertainty behind the magnitude of effect associated with this TRV. Also, unfortunately, it would not be possible to develop a dose-response curve from the toxicological data in the underlying study because there was only one PCB dose level tested (Wren *et al.*, 1987). Given the complexities of trying to characterize effects of complex mixtures, this TRV is focused on toxicity of coplanar PCB congeners, which share a similar mode of action (CCME, 2001a). However, it is recognized that other PCB congeners (i.e., non-coplanar PCBs) may be missed with this approach. If dioxins and furans are also a contaminant of interest on site in addition to PCBs, then consideration of PCBs along with dioxins and furans is recommended (as per CCME, 2001a), as these chemical groups share a common mode of action.

Evaluation of candidate TRVs

Table A.30. Candidate mammalian toxicity reference values (TRVs) for polychlorinated biphenyls (PCBs)

Candidate TRV (ng TEQ/kg bm/day)	Source (See Reference Section 3)
0.19	**CCME, 2001a**

There are other TRVs for specific PCB mixtures that have been presented in various sources. For example, CEAEQ (2012) presents mammalian TRVs based on toxicity of Aroclor 1254, and Sample *et al.* (1996) presents mammalian TRVs for Aroclor 1016, 1242, 1248, and 1254. However, these and other TRVs were not considered as candidate TRVs or included in Table A.30 above because of uncertainties and complexities involved in comparing toxicological data for PCB mixtures of different compositions. Individual PCB congeners can vary in toxicity by up to many orders of magnitude (CCME, 2001a). Therefore, different mixtures composed of different congeners will also vary in their toxicity. Acute mammalian toxicity to PCBs generally increases with decreasing chlorination, which is opposite to the relationship observed in birds (CCME, 2001a). Estimated doses for mammalian PCB toxicity as reported in Appendix XIV of Environment Canada (2001) ranged from 0.008 mg/kg bm/day to 31 mg/kg bm/day for a variety of PCB formulations (e.g., different Aroclor formulations), species (e.g., mice, rabbits, bats, mink), endpoints (e.g., biochemical, reproduction, survival), and effect levels (ranging from NOAELs to 100% mortality). The selected TRV from CCME (2001a) was the only available TRV that evaluated toxicity data for a range of different PCB mixtures with varying compositions, by applying a toxic equivalency approach (Van den Berg *et al.*, 1998).

Suggestions for improved future TRVs

There are a wide range of mammalian PCB toxicity data available, but there were no available mammalian TRVs for PCBs that readily integrated toxicity data across multiple studies, species, or endpoints. Therefore, future effects assessments for PCBs could benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) to existing PCB toxicological data. Effects characterization (and overall risk assessment) may be enhanced by considering a range of toxicity studies that are relevant to site-specific receptors and PCB mixture compositions present on site. For example, graphical exploration of available dose-response data and quantification of magnitude of effect size across multiple toxicological studies, species, endpoints, and mixture compositions (e.g., methods as illustrated in Hill *et al.*, 2014) will likely improve the overall effects characterization and assessment within an ERA, especially compared to relying on a single TRV. Other types of information, such as effects measures based on diet concentration or tissue concentration, may also be investigated to further supplement and improve ecological risk assessments of PCBs within a weight-of-evidence approach.

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) [Dioxins and Furans]

Receptor: Mammals

Selected TRV = 0.17 ng TEQ/kg bm/day
Source: CCME, 2001b
Grade: C

This TRV is also the basis for the current Canadian Tissue Residue Guideline for the Protection of Wildlife Consumers of Aquatic Biota (CCME, 2001b). Complete details on the derivation of this value are provided in CCME (2001b). It should be noted that the TRV for dioxins and furans is expressed in **units of ng toxic equivalency units (TEQs)/kg bm/day**. This TRV is based on the geometric mean of the NOAEL and LOAEL for growth rates in guinea pigs fed 2,3,7,8-TCDD in their diet over a 90-day exposure period in a toxicological study by De Caprio *et al.* (1986). An uncertainty factor of 10 was applied to the geometric mean of the NOAEL and LOAEL to adjust from subchronic to chronic exposure duration and to accommodate differences in interspecies sensitivities to PCDD/Fs.

Merits of the selected TRV

The toxicological study was selected by CCME (2001b) from a broad set of available toxicological studies that included a range of species (e.g., at, guinea pigs, hamsters, mink). This TRV is also based on a relevant reproductive endpoint (growth of pups), as well as liver weight. As a unique issue to dioxin/furan TRVs, development of this TRV involved application of toxic equivalency factors (TEFs), as recommended by the World Health Organization (van den Berg *et al.*, 1998), so that varying toxicities of different dioxin and furan congeners within mixtures could be accounted for (see CCME, 2001b, for a description of TEFs and how they were applied in this TRV).

Limitations of the recommended default TRV

The magnitude of effect associated with this TRV is not quantified because the TRV was derived as the geometric mean of a NOAEL and LOAEL value and divided by an uncertainty factor of 10 to account for interspecies sensitivities to dioxins and furans. The LOAEL used in the geometric mean behind this selected TRV was associated with up to 39% reduced growth rate in the male guinea pig pups (22% reduction in female pups), which on its own would be considered too severe for a FCSAP default TRV to provide a level of protection consistent with no more than minimal to low level of effects. The NOAEL that was used in the geometric mean behind this TRV was an experimental treatment level (i.e., the NOAEL did not need to be calculated from the LOAEL). Therefore, there is uncertainty about the magnitude of effect associated with this TRV. Given the complexity of trying to characterize the effects of complex mixtures, this TRV is focused on toxicity of 2,3,7,8-substituted PCDD/F congeners, which share a similar mode of action and are thought to elicit most or all of the toxicity of dioxins and furans (CCME, 2001b). However, it is recognized that other dioxin and furan congeners may be missed with this approach, and their toxicity is not well studied. If both PCBs and dioxins and furans are contaminants of interest on site, these groups of chemicals should be evaluated together given the shared mode of action between the coplanar PCB congeners and the 2,3,7,8-substituded PCDD/Fs.

Evaluation of candidate TRVs

Table A.31. Candidate mammalian toxicity reference values (TRVs) for dioxins and furans

Candidate TRV (ng TEQ/kg bm/day)	Source (See Reference Section 3)
0.17	**CCME, 2001b**

The selected TRV has various merits and limitations (described above). CCME (2001b) presented this TRV following a comprehensive review of available toxicological data, and it can therefore be used as a default value for FCSAP. CCME (2001b) also summarized a broader set of available toxicological data for PCDD/Fs. Because of the uncertainties inherent in assessing the toxicity of a mixture of chemicals like PCDD/Fs (on top of other generic limitations of TRVs), consideration to as broad a set of toxicity data as possible (e.g., as summarized in CCME, 2001b) should be given on a site-specific basis when selecting a TRV or methods for effects assessment that is best suited for specific receptors of concern, especially where risk at a site is being driven by this contaminant.

Suggestions for improved future TRVs

Most mammalian dioxin/furan toxicity data that are available are focused on 2,3,7,8-TCDD (CCME, 2001b), which is thought to be one of the most toxic PCDD/Fs. Future effects assessments for dioxins and furans could benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) to existing PCDD/F toxicological data. Given the additional complexities of mixtures, careful TRV selection on a site-specific basis is likely required for PCDD/Fs. Considering the complexities and uncertainties unique to assessing complex PCDD/F mixtures, effects characterization (and overall risk assessment) may be enhanced by considering a range of toxicity studies that are relevant to site-specific receptors and dioxin and furan congeners present on site. For example, graphical exploration of available dose-response data and quantification of the magnitude of effect size across multiple toxicological studies, species, endpoints, and mixture compositions (e.g., methods as illustrated in Hill *et al.*, 2014) will likely improve the overall effects characterization and assessment within an ERA, especially as compared to relying on a single TRV. This type of approach for assessing effects (e.g., as described by Hill *et al.*, 2014) is an alternative to a single-TRV-based approach and is considered consistent with existing FCSAP TRV guidance (FCSAP, 2012b) and ERA guidance (FCSAP, 2010). Other types of information, such as effects measures based on diet concentration or tissue concentration, may also be investigated to further supplement and improve ecological risk assessments of dioxins and furans within a weight-of-evidence approach.

A.3. Selected Avian Toxicity Reference Values: Supporting Scientific Rationale

Arsenic [Metalloid]

Receptor: Birds

Selected TRV = 4.4 mg/kg bm/day
Source: CEAEQ, 2012
Grade: A

Basis for the selected TRV

The selected TRV was derived by CEAEQ (2012), which calculated an EC_{20} for each of eight different studies reporting reproduction, growth, and mortality endpoints for mallard ducks, chickens, and quails. Uncertainty factors were applied to the calculated EC_{20}s to account for toxicity tests of short exposure durations and for mortality endpoints. EC_{20}s were divided by an uncertainty factor of 2 for studies considered to have short test durations. Those EC_{20}s based on a survival endpoint were also divided by an uncertainty factor of 5. Therefore, the highest total uncertainty factor applied to any one study in CEAEQ (2012) was 10. The selected TRV is the second lowest EC_{20} of the eight evaluated by CEAEQ (2012). The toxicity study underlying this EC_{20} observed reduced growth rates in chickens (*Gallus domesticus*) exposed to arsenic via ingestion for 16 days.

Merits of the selected TRV

CEAEQ (2012) quantified the effect level at 20% for the underlying toxicity data and can therefore confirm that this TRV is based on a study that provides a level of protection consistent with a minimal to low level of effects. There were five experimental treatment levels (including a control) in the underlying toxicological study (Czarnecki, 1984). The EC_{20} was calculated to be just below the first treatment level. CEAEQ (2012) also gave the underlying study a high level of confidence. Multiple toxicity studies (n=8) were used in the TRV derivation, although four of the studies were given a low level of confidence" by CEAEQ (2012). Other merits include appropriate biological endpoints, study durations ranging from acute to chronic, and the fact that ingestion is the exposure pathway.

Limitations of the recommended default TRV

The selected TRV was derived from data for a limited number of avian species (ducks, chickens, or quails), which may not be protective of all birds. The application of an uncertainty factor (of 2) to account for acute exposure duration (16 days) in underlying toxicity tests adds an element of uncertainty to the derivation process, as these factors have unknown implications for the level of protection provided by this TRV.

Evaluation of candidate TRVs

Table A.32. Candidate avian toxicity reference values (TRVs) for arsenic

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
2.24	USEPA, 2005a
2.46	USEPA, 1999
3.7	Rae, 2013
4.4	**CEAEQ, 2012**
4.5	Rae, 2013
5.5	USEPA Region 9, 2009
5.6	CEAEQ, 2012
7.38	Sample *et al.*, 1996
12.84	Sample *et al.*, 1996
47.6	CCME, 1997b

A total of 10 different avian TRVs for arsenic, ranging from 2.24 to 47.6 mg/kg bm/day, were evaluated. The majority of the available TRVs were numerically close together. The selected TRV (4.4 mg/kg bm/day) fell between the two TRVs from Rae (2013) that are based on a geometric mean of either NOAELs or LOAELs for growth, reproduction and survival endpoints in the USEPA dataset. This comparison across candidate TRVs provides additional evidence that the selected TRV provides an appropriate level of protection (despite uncertainties arising from use of uncertainty factors).

Overall, avian toxicology data for arsenic was somewhat limited. Approximately 10 unique studies were identified across all evaluated TRVs. Only a few of these studies reported bound effect levels (i.e., several studies reported only unbound NOAELs). However, two of three growth-based LOAELs (all unbound) in the USEPA dataset (2005a) were below the selected TRV. These LOAEL data suggest that effects may be observed below the selected TRV. However, quantification of the effect size associated with these LOAEL data has not been evaluated. Other LOAEL-based data (i.e., TRVs from Sample *et al.*, 1996: 7.38 and 12.8 mg/kg bm/day) were above the selected TRV and are associated with ≤25% effect level. However, they are both based on survival endpoints and do not consider any information on growth or reproduction.

Suggestions for improved future TRVs

Future avian arsenic TRV development would benefit from investigations into any potential additional and/or more recent toxicological data, particularly toxicological data for species or categories of birds not yet included in existing TRVs. Future avian arsenic TRV development would also benefit from the application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b), particularly dose-response methodology that can enhance the depth of toxicological information across a broad range of studies, species, and endpoints used to inform risk assessments to birds from arsenic exposure. However, the selected TRV is considered likely to provide a sufficient level of protection and to be associated with no more than minimal to low effects to common species.

Barium [Metal]

Receptor: Birds

Selected TRV = 51.3 mg/kg bm/day
Source: CEAEQ, 2012
Grade: B

Basis for the selected TRV

The selected default TRV is derived by CEAEQ (2012) using Weibull statistical methods to model a dose-response curve for mortality from a single underlying study, Johnson and Titus(1960), in which barium toxicity to chickens (unspecified species) was tested over a 4-week exposure to barium hydroxide in their diet. No allometric scaling was used to calculate this TRV, but an uncertainty factor of 10 was applied by CEAEQ (2012) to account for mortality endpoint and acute exposure duration.

Merits of the selected TRV

The selected TRV applied dose-response methods, which are consistent in part with methods generally recommended by FCSAP. Dose-response methods allow for the selection of a TRV at the 20% effect level, which is consistent with the level of protection targeted for default wildlife TRVs for FCSAP (e.g., no more than minimal to low effects to common species). Other merits include a relevant biological endpoint (survival), which can be extrapolated to population-level effects, and the large number of tested dose levels between 250 and 32,000 ppm Ba in the diet (between 5 and 100% mortality observed in the four highest dose levels; no effect on mortality observed in the lowest four dose levels).

Limitations of the recommended default TRV

The main limitation associated with this TRV is an overall lack of available avian toxicity data for barium. Only two toxicological studies were represented across all available TRVs (Johnson and Titus, 1960). Therefore, only a single avian species (chicken) and single endpoint (survival) are represented by the TRV, and there is no information available to provide an understanding of how well this TRV may protect other endpoints (e.g., reproduction, growth) or other avian species. The 4-week exposure duration in the underlying toxicological study may be too short to accurately represent long-term exposure durations at federal contaminated sites. This short test duration was also the basis for CEAEQ's assessment of "low confidence" in this TRV (2012; supporting documentation). Another limitation associated with this TRV is the use of an uncertainty factor with no clear scientific rationale reported. Uncertainty factors are generally not recommended by FCSAP unless scientific support can be demonstrated.

Evaluation of candidate TRVs

Table A.33. Candidate avian toxicity reference values (TRVs) for barium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
20.8	Sample *et al.*, 1996; Allaway and Stodola, 2011
41.7	OMOE, 2009
51.3	**CEAEQ, 2012**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

All three TRVs that were evaluated for the purposes of selecting a default value for FCSAP (Table A.32) were based on the same underlying toxicological data (Johnson and Titus, 1960). The TRVs from Sample *et al.* (1996; 20.8 mg/kg bm/day) and from OMOE (2009; 41.7 mg/kg bm/day) represent the NOAEL and LOAEL for chicken survival in Johnson and Titus (1960). The TRV from CEAEQ (2012; 51.3) represents the 20% effect size in Johnson *et al.* (1960), calculated using a Weibull statistical dose-response model. Despite the large number of data points (8 dose levels tested) in the underlying toxicity test, a default FCSAP TRV is ultimately limited by a lack in breadth of available barium toxicity information for birds.

Suggestions for improved future TRVs

Updated literature searches for additional toxicology data may help supplement the currently limited set of available data. In addition, further investigation into the currently available underlying toxicological data (i.e., dose-response data) could quantitatively integrate and enhance the utility of the limited toxicity data. For example, Johnson and Titus (1960) is also cited in CCME (2013): CCME suggests a growth endpoint was also measured in Johnson and Titus (1960). Therefore, it may be worth exploring the original citation (Johnson and Titus, 1960) to incorporate data for an additional endpoint (growth) into future TRV derivation. However, these growth data are likely to be strongly related to existing survival data because they are from the same study as existing TRVs. Therefore, TRVs and toxicological data for additional avian species should also be investigated and evaluated when available, and/or on site-specific basis.

Cadmium [Metal]

Receptor: Birds

Selected TRV = 2.1 mg/kg bm/day
Source: CEAEQ, 2012
Grade: B

Basis for the selected TRV

The selected default value is derived by CEAEQ (2012) using Weibull statistical methods to model a dose-response curve for mortality from six underlying toxicological studies. The dose corresponding to a 20% effect level (EC_{20}) was interpolated from dose-response curves for each of the six studies. EC_{20}s from sub-acute or acute toxicity tests were divided by an uncertainty factor of 2 (to approximate a chronic exposure duration). In addition, EC_{20}s based on survival effects were divided by an uncertainty factor of 5 (to account for the severity of a mortality endpoint). Therefore, the highest total uncertainty factor applied to any one study in CEAEQ (2012) was 10. The lowest resulting EC_{20} was from Richardson (1974, as cited in CEAEQ, 2012, supporting documentation) and described effects to juvenile quail growth of a 4-week exposure to cadmium in food. Overall, the six studies considered by CEAEQ (2012) included data for four species (quails, chickens, pheasants, and mallard ducks) and three endpoints (juvenile growth, reproductive endpoints, and survival).

Merits of the selected TRV

The selected TRV applied dose-response methodology, which is consistent in part with FCSAP recommendations for TRV development. Dose-response methods allow for the selection of a TRV at the 20% effect level, which provides a level of protection consistent with a minimal to low level of effects. Other merits include use of a relevant biological endpoint (growth of juveniles) that can be extrapolated to population-level effects and use of a variety of different studies (six).

Limitations of the recommended default TRV

One limitation associated with this TRV is the use of uncertainty factors, which have an unknown effect on the level of effect associated with the TRV. In general, uncertainty factors are not recommended by FCSAP unless scientific support can be demonstrated. The 4-week exposure duration in the underlying toxicological study may be too short to accurately represent long-term exposure durations at federal contaminated sites. This short test duration was also the basis for CEAEQ's assessment of "low confidence" in this TRV (2012; supporting documentation). This TRV was interpolated from a Weibull model and only two data points: a 0% response in the control and a 38% response in the single treatment level (at 10.31 mg/kg bm/day) tested in Richardson (1974, cited in CEAEQ, 2012).

Evaluation of candidate TRVs

Table A.34. Candidate avian toxicity reference values (TRVs) for cadmium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.7	USEPA Region 9 BTAG, 2009
1.0	USEPA Region 9 BTAG, 2009
1.45	Sample *et al.*, 1996
1.47	USEPA, 2005c; Dillon, 2013
2.1	**CEAEQ, 2012**
3.07	OMOE, 2009; CCME, 1996b; Allaway and Stodola, 2011
3.1	Rae, 2013
3.5	CEAEQ, 2012
7.8	Rae, 2013
10.4	USEPA Region 9 BTAG, 2009
20	Sample *et al.*, 1996

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Eleven TRVs, ranging from 0.7 to 20 mg/kg bm/day, were evaluated. The TRV from USEPA (2005c; 1.47 mg/kg bm/day) was based on the largest number of studies (93 results from 35 studies) for multiple relevant endpoints (reproduction, growth, and survival) and a variety of species (chickens, mallards, wood ducks, Peking ducks, black ducks, quails, and starlings), and they did not apply uncertainty factors. The 3.1 mg/kg bm/day TRV from Rae (2013) is based on a subset of data in the USEPA dataset; it is the geometric mean of all reproductive, growth, and survival NOAELs in the USEPA dataset, and no uncertainty factors were applied to it either. The selected TRV of 2.1 mg/kg bm/day (CEAEQ, 2012) falls in between the USEPA (2005c) TRV and the NOAEL-based TRV (Rae, 2013), providing additional evidence that the selected TRV from CEAEQ (2012) likely provides a level of protection consistent with a minimal to low level of effects for a variety of avian species, in a variety of exposure conditions. The higher TRV from Rae (2013; 7.8 mg/kg bm/day) is the geometric mean of all reproduction, growth, and survival LOAELs from the USEPA dataset. However, this TRV was developed for remediation and detailed risk management objectives, and without additional analysis to quantify the level of protection provided by this LOAEL-based TRV, it is not considered protective enough to meet a more conservative, screening-level of protection consistent with a minimal to low level of effects for all birds.

The remaining TRVs that were evaluated were not selected for a variety of reasons. Although all TRVs met some FCSAP criteria, several were not selected because of uncertainties in effect size associated with the underlying NOAEL or LOAEL, which may potentially be too high for FCSAP, and uncertainties in context with respect to multiple studies, endpoints, or species for those TRVs based on single studies. TRVs with the limitation of being based on a NOAEL or LOAEL from a single study include TRVs from Sample *et al.* (1996; 1.45 and 20 mg/kg bm/day) and from USEPA Region 9 BTAG (2009; 0.7 and 1.0 mg/kg bm/day). Three TRVs were not selected because they were derived from toxicity data showing too severe of an effect level for a default value for FCSAP. The TRV from OMOE (2009; 3.07 mg/kg bm/day), was associated with 39% reduced egg production in one study. The TRV from CEAEQ (2012; 3.5 mg/kg bm/day) was associated with a 40% effect level for reduced growth of juvenile quail in one study. Insufficient information was available to complete a full evaluation of the TRV from USEPA Region 9 BTAG (2009; 10.4 mg/kg bm/day), but it was described as representing a “mid-range of

reproductive effects" and "would be expected to produce an adverse effect to an individual or population of organisms." It was therefore also considered too severe for a default value for FCSAP.

All of the evaluated TRVs did have a variety of merits, including relevant endpoints and species considered. However, most were derived from single toxicity studies and lacked quantification of underlying effect size. The TRVs from USEPA (2005c) and CEAEQ (2012) had additional merits over the other TRVs in that they considered a wide variety of studies. Furthermore, the CEAEQ (2012) applied dose-response methodology and was therefore was considered most appropriate for FCSAP at this time.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying available TRVs (e.g., both USEPA dataset, and studies in the CEAEQ dataset) and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV with a quantitatively informed level of protection. Further investigation may also include review of any additional avian TRVs or toxicological data were available, and/or on site-specific basis where the need arises.

Chromium (hexavalent) [Metal]

Receptor: Birds

Selected TRV = 16 mg/kg bm/day
Source: Condor *et al.*, 2009
Grade: C

Basis for the selected TRV

The selected default value is from a study by Butkauskas and Sruoga (2004), as cited in Condor *et al.* (2009). This TRV is based on an unbound NOAEL for Japanese quail hatching success in a 12-week toxicity test exposing male quail to hexavalent chromium through their diet. Although not significantly different from the control, the NOAEL treatment group was associated with 14% reduction in egg hatching success relative to control.

Merits of the selected TRV

The selected TRV is based on a reproductive endpoint (quail egg hatching success) that is relevant to population-level dynamics. A review of the original study (Butkauskas and Sruoga, 2004) confirmed that this TRV is associated with a sufficiently conservative level of effect to provide a level of protection consistent with a minimal to low level of effects.

Limitations of the recommended default TRV

The selected TRV is based on a single study for a single species, and there is therefore a high degree of uncertainty when applying this TRV to represent a broad range of species and exposure conditions relevant to federal contaminated sites. Furthermore, this TRV is based on an unbound NOAEL, which also carries a high degree of uncertainty because no adverse effects were observed at any experimental treatment level in the underlying toxicity test, and it is not possible to develop a dose-response curve based on this single study. A review of Butkauskas and Sruoga (2004) also revealed that the primary objective of this underlying toxicity study was focused on comparing sensitivity between different genotypes of Japanese quail, and not on studying the dose-response relationship between hexavalent chromium and adverse effects to birds.

Evaluation of candidate TRVs

Table A.35. Candidate avian toxicity reference values (TRVs) for hexavalent chromium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
11	LANL 2014; Allaway and Stodola, 2011; Dillon, 2013.
16	**Condor *et al.*, 2009**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Two avian TRVs for hexavalent chromium were available for review. Therefore, there is limited information available at this time to evaluate the selected TRV (based on a single toxicological study) within the context of a broader range of information about a variety of species, endpoints, or exposure conditions as is relevant for FCSAP goals.

The TRV of 11 mg/kg bm/day from LANL (2014) is based on an unbound NOAEL for growth and survival in a 32-day toxicity test exposing chickens to hexavalent chromium in their food (Romoser *et al.*, 1961). No allometric scaling or uncertainty factors were used to calculate this TRV. There was insufficient information in the toxicity study (Romoser *et al.*, 1961) underlying the LANL (2014) TRV to quantify the magnitude of toxicological response or to extract any dose-response information. It is therefore difficult to evaluate the level of protection that would be provided to FCSAP sites if this TRV were to be applied. A review of Romoser *et al.* (1961) also revealed that the primary objective of this underlying toxicity study was focused more on vanadium toxicity, rather than hexavalent chromium toxicity.

USEPA (2008) reported avian toxicity data for hexavalent chromium from four unique studies (Asmatullah and Noreen, 1999; Jensen and Maurice, 1980; Rao *et al.*, 1983; Romoser *et al.*, 1961), but this dataset did not meet its minimum data requirements for deriving a TRV. However, the hexavalent chromium toxicity data reported in USEPA (2008) can still be used to further assess existing TRVs. For example, the NOAELs for reproduction, growth, and survival in USEPA (2008) ranged between 0.024 and 8.59 mg/kg bm/day. Only one LOAEL was reported for survival, growth, or reproductive endpoints at 4.02 mg/kg bm/day for growth and reproduction (Asmatullah and Noreen, 1999; unbound LOAEL).

Suggestions for improved future TRVs

The selected default TRV is based on an unbound NOAEL, which is generally not recommended by FCSAP (2010b) for developing TRVs, because it represents toxicity tests in which no adverse effects were observed at any of the tested dose levels. Therefore, this TRV may be overly conservative. Furthermore, there are no additional data available that can be used to put these TRVs into a broader context for multiple species, endpoints, and ecologically relevant exposure conditions. To improve future effects assessments of hexavalent chromium to birds, updated literature searches for additional toxicology data (e.g., data cited in USEPA, 2008) may help supplement the currently limited set of available data. Future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. Other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments of hexavalent chromium within a weight-of-evidence approach.

Chromium (total) [Metal]

Receptor: Birds

Selected TRV = 2.66 mg/kg bm/day
Source: USEPA, 2008
Grade: C

Basis for the selected TRV

The selected default value is from USEPA (2008) and represents the geometric mean of 12 NOAELS for reproduction or growth, 10 of which are unbound. Underlying toxicity tests considered three test species (mostly chicken, but also turkey and black duck) exposed to trivalent chromium in their diet for anywhere from 1 week to 10 months. Survival endpoints were also considered in the USEPA (2008) dataset, but not included in the geometric mean. Note that trivalent chromium is the chemical form used in most underlying toxicity tests on the assumption that the majority of total chromium that receptors would be exposed to is trivalent form.

Merits of the selected TRV

The selected TRV was derived from multiple toxicological studies (10) and therefore reflects the broad range of exposure conditions and receptors more so than a TRV derived from a single toxicological study. Three species of birds were tested in these studies, thus providing a better representation of a variety of bird species, compared to TRVs based on single species from a single study. The TRV considered relevant toxicological data (acceptable biological endpoints of reproduction, growth, and survival, a range of exposure durations, and an exposure pathway through contaminated food and water), and no allometric scaling or uncertainty factors were applied during TRV derivation.

Limitations of the recommended default TRV

The selected TRV may potentially be overly conservative for FCSAP because the majority of the NOAELs used to calculate the geometric mean are unbound. Bound NOAELs are preferred because they represent toxicity tests in which adverse effects were actually observed. In addition, there were no LOAELs for reproduction, growth, or survival reported in USEPA (2008) that were below the selected TRV, further suggesting that this NOAEL-based TRV from USEPA (2008) is potentially overly conservative. There is also low confidence in the selected TRV for total chromium (2.66 mg/kg bm/day) because it is lower than the selected TRV for hexavalent chromium (11 mg/kg bm/day), which is thought to be more toxic. It would be expected that there would be a higher TRV for total chromium, the less toxic form of the contaminant. This observation likely reflects the limited dataset for both total and hexavalent chromium avian toxicity. Additional concerns with an overly conservative TRV stem from the fact that trivalent chromium is a micronutrient, so there may be ecological consequences for recommending a TRV that is too low.

Evaluation of candidate TRVs

Table A.36. Candidate avian toxicity reference values (TRVs) for total chromium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
1.0	CEAEQ, 2012
2.66	**USEPA, 2008; Dillon, 2013**
5.0	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

The TRV from Sample *et al.* (1996; 5.0 mg/kg bm/day) was based on a reproductive LOAEL for black ducks exposed to trivalent chromium in their diet and was therefore relevant for FCSAP. However, it had two limitations that precluded its selection as a default TRV for FCSAP: (i) it was based on a single study and it is therefore uncertain how representative it is of multiple species and exposure conditions; and (ii) it was based on unpublished data (Haseltine *et al.*, as cited in Sample *et al.*, 1996), so it is uncertain whether the effect size associated with this LOAEL-based TRV will provide a sufficient level of protection. The TRV from CEAEQ (2012; 1.0 mg/kg bm/day) was based on the corresponding NOAEL from Haseltine *et al.* (unpublished data) and therefore includes the same limitations as the TRV from Sample *et al.* (1996; e.g., single study, unquantified effect size). Data from Haseltine *et al.* (unpublished) was also cited in the USEPA (2008) dataset (at a value of 2.8 mg/kg bm/day for the reproductive LOAEL). However, the USEPA (2008) TRV was evaluated as better meeting FCSAP TRV criteria than the other two available candidate TRVs because it considered multiple studies and a broader range of toxicity data than the Sample *et al.* (1996) TRV.

Suggestions for improved future TRVs

Overall, there is somewhat limited available toxicological data. Furthermore, none of the available NOAEL or LOAEL data for reproduction, growth, or survival endpoints in the USEPA dataset were bound, which indicates uncertainty with the level of protection provided by the selected default TRV, as well as an overall limited understanding of the characterisitcs of the dose-response relationship for total chromium.. Therefore, extraction of dose-response data from underlying toxicological studies may facilitate development of an improved TRV. Additionally, updated literature searches for additional toxicology data may help supplement the currently limited set of available data. Derivation of new TRVs should apply FCSAP-recommended methodology for TRV development.

Copper [Metal]

Receptor: Birds

Selected TRV = 4.5 mg/kg bm/day
Source: CEAEQ, 2012
Grade: A

Basis for the selected TRV

The selected default value is derived by CEAEQ (2012) using Weibull statistical methods to model dose-response curves for five different studies. The dose corresponding to a 20% effect level (EC_{20}) was interpolated from dose-response curves for each of these five studies. All EC_{20}s were divided by an uncertainty factor of 2 to account for duration of the underlying toxicity test, which ranged from 14 to 70 days. The lowest EC_{20}, which was from Stevenson and Jackson (1980), was selected as a TRV by CEAEQ (2012). All five studies considered by CEAEQ (2012) investigated the effects of copper in the diet on reproductive endpoints in chickens. The selected EC_{20} was based on an endpoint of number of eggs laid in a 48-day test.

Merits of the selected TRV

The selected TRV was derived using dose-response methods, which is consistent with the methodology generally recommended by FCSAP. Dose-response methods allow for the selection of a TRV at the 20% effect level, which provides a level of protection consistent with a minimal to low level of effects. Other merits include a relevant biological endpoint (reproduction), which can be extrapolated to population-level effects, and consideration of a number of studies (five). CEAEQ also assigned "high confidence" to this TRV based on its evaluation of the quality and relevance of the underlying toxicity data.

Limitations of the recommended default TRV

The selected TRV from CEAEQ (2012) only considered data for a single species, chicken, and it is therefore uncertain how well this TRV may apply to multiple avian species other than chicken. Another limitation associated with this TRV is the use of an uncertainty factor, which obscures the level of protection provided by the selected TRV. Uncertainty factors are generally not recommended by FCSAP unless scientific support can be demonstrated.

Evaluation of candidate TRVs

Table A.37. Candidate avian toxicity reference values (TRVs) for copper

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
4.05	USEPA, 2007a; Dillon, 2013
4.5	**CEAEQ, 2012**
5.23	CCME, 1997b; Allaway and Stodola, 2011
20	Rae, 2013
22.9 [2]	USEPA Region 9 BTAG, 2009;
37	Rae, 2013
46.97	USEPA, 1999
61.7	Sample *et al.*, 1996; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.
2. This value represents the "Unadjusted dose" (i.e., without uncertainty factors), as presented in USEPA Region 9 BTAG (2000). The USEPA Region 9 BTAG (2009) avian TRV for copper is 2.3 mg/kg bm/day, which includes an uncertainty factor of 10 for subchronic to chronic conversion.

Eight TRVs, ranging from 4.05 to 61.7 mg/kg bm/day, were evaluated. The selected TRV from CEAEQ (2012; 4.5 g/kg bm/day) represents the 20% effect size in Stevenson and Jackson (1980), calculated using a Weibull statistical dose-response model, but the associated effect size is obscured by the use of an uncertainty factor (of 5). Although the selected TRV was based on data for a single species only, the TRV from USEPA (2007a; 4.05 mg/kg bm/day) was based on a large number of studies (393 results from 107 studies) for multiple relevant endpoints (reproduction, growth, survival) and multiple species (mostly chicken, but also turkey and duck). The USEPA avian TRV for copper was the highest bound NOAEL below the lowest bound LOAEL for reproduction and growth endpoints in that large dataset. Therefore, the USEPA (2007a) TRV provides additional evidence that the selected TRV from CEAEQ (2012) likely provides a level of protection consistent with a minimal to low level of effects to a variety of avian species in a variety of exposure conditions. Furthermore, the geometric mean of all survival, growth, and reproduction NOAELs in the USEPA (2007a) dataset equals 20 mg/kg bm/day (Rae, 2013) and provides some evidence that the selected TRV is at the low end at the distribution of a range of NOAELs and may therefore potentially provide a level of protection well below a 20% effect level.

The remaining TRVs that were evaluated were not selected for a variety of reasons. The highest TRV (61.7 mg/kg bm/day from Sample *et al.*, 1996) was associated with 30% reduced chick growth, the LOAEL dose-level in one study (Mehring *et al.* 1960), which is too severe an effect level for a default FCSAP value, and therefore this TRV was not selected. The TRV from USEPA (46.97 mg/kg bm/day) was also based on Mehring *et al.* (1960), but on the NOAEL dose-level. Without further analysis of the underlying toxicological data, it is unknown whether the effect size associated with that NOAEL is sufficiently lower than the 30% effect size at the LOAEL to provide a level of protection that is consistent with a minimal to low level of effects; therefore, it was not selected as a FCSAP default. The TRV from USEPA Region 9 (2009; 22.9 mg/k) could not be selected because there was not enough information available for a complete evaluation. The TRV from CCME (1997b; 5.23 mg/kg bm/day) was evaluated and met some criteria, including the fact that it was based on a bound LOAEL for a relevant endpoint (growth) and species (hen). However, there were other TRVs that had additional merits that made them more suitable than a TRV based on a single study and single species with no quantified effect size associated with the underlying LOAEL.

Suggestions for improved future TRVs

Given the context provided by the broad toxicity dataset in USEPA (2007a) and the dose-response method applied by CEAEQ (2012), the level of protection provided by the selected TRV is considered likely to be associated with no more than minimal to low level of effects to common species. There is some evidence (e.g., the geometric mean of survival, growth, and reproduction NOAELS from the Rae, 2013 TRV is four-times the selected TRV) that the selected CEAEQ (2012) TRV may potentially be overly conservative. Therefore, future TRV development that applies dose-response methodology as recommended by FCSAP (2010b) may result in an improved default TRV.

Free Cyanide [Inorganic]

Receptor: Birds

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable as default values for FCSAP

Table A.38. Candidate avian toxicity reference values (TRVs) for cyanide

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.04	LANL, 2014
0.21	CCME; 1996b; OMOE, 2011; Allaway and Stodola, 2011; Dillon, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Only two TRVs were available for review, both of which were based on Wiemeyer *et al.* (1986), who report an LD50 for a single dose of cyanide to American kestrel. LD50 values represent a severe effect level, which does not provide a level of protection that is consistent with a minimal to low level of effects, and the acute nature of the study does not represent chronic exposure conditions in the environment. Uncertainty factors of 20 and 100 were applied to derive TRVs of 0.21 and 0.04 mg/kg bm/day, respectively. No scientific rationale was provided to justify the selection of the uncertainty factors or to demonstrate that the TRVs would be protective of all birds. Furthermore, the TRVs are derived from a single study on a single bird species, so their application across a wide range of avian species is not justified. Given the uncertainties and concerns associated with both TRVs, neither could be selected as a default TRV for FCSAP at this time.

Suggestions for improved future TRVs
On the basis of the criteria established for this project, none of the available candidate TRVs were considered appropriate or sufficient for FCSAP. Avian cyanide toxicity data is limited, and future work should involve a thorough literature review to source new data that will allow for the derivation of a new TRV that is consistent with FCSAP TRV derivation guidance outlined in module 2. Examples of sources to consult include Donato *et al.* (2007), Griffiths *et al.* (2014), Henny *et al.* (1994), and the International Cyanide Management Institute (2015).

Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Lead [Metal]

Receptor: Birds

Selected TRV = 1.63 mg/kg bm/day
Source: USEPA, 2005d
Grade: B

Basis for the selected TRV

The selected TRV is derived from an USEPA dataset of 54 studies and is the highest bound NOAEL that is lower than the lowest bound LOAEL. The dataset includes toxicity tests conducted on a variety of avian species (chicken, mallard, kestrel, zebra finch and quail), and the selected TRV is therefore deemed representative of a diversity of avian species. Biological endpoints assessed in toxicity tests across the dataset include reproduction, growth and mortality.

Merits of the selected TRV

The TRV selected through the USEPA derivation process comes from Edens and Garlich (1983), who exposed chickens to various doses of lead acetate (0, 1, 10 and 100 ppm) through their diets for 4 weeks. Neither allometric scaling nor uncertainty factors were used in the derivation of this TRV. As a whole, the USEPA considered a number of relevant biological endpoints, and the depth of data considered in the development of this TRV therefore reflects a broad range of environmental exposure conditions and receptors.

Limitations of the recommended default TRV

USEPA uses a NOAEL-based approach to derive TRVs, which could lead to the TRV being overly conservative for FCSAP objectives. However, in the USEPA dataset, two unbound LOAELs were lower than the selected TRV, demonstrating that some effects may still occur.

Evaluation of candidate TRVs

Table A.39. Candidate avian toxicity reference values (TRVs) for lead

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.014	USEPA Region 9 BTAG, 2009
1.1	CEAEQ, 2012
1.63	**USEPA, 2005d**
3.85	Sample *et al.*, 1996
11.3	Sample *et al.*, 1996; Allaway and Stodola, 2011; Dillon, 2013
16	Rae, 2013
28	OMOE, 2009; Allaway and Stodola, 2001; Dillon 2013
52	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Eight TRVs were evaluated by FCSAP, with values ranging from 0.014 to 52 mg/kg bm/day. Two TRVs (0.014 and 11.3 mg/kg bm/day) were not selected because it was not immediately clear from the primary literature whether or not they provide a level of protection that is consistent with a minimal to low level of effects (i.e., less than 25% effect level). Three other candidate TRVs were based on NOAELs

from limited datasets, and there is therefore uncertainty regarding their applicability to a broad range of species, endpoints, and exposure conditions. The TRVs of 3.85 mg/kg bm/day (Sample *et al.* 1996) and 28 mg/kg bm/day (OMOE, 2009) were each based on a single study. The 1.1 mg/kg bm/day TRV was the lower of two separate studies evaluated by CEAEQ (2012). Without further analysis, the level of protection provided by these TRVs is also not quantified.

The remaining three TRVs are based on the USEPA dataset and represent the highest bound NOAEL below the lowest bound LOAEL (1.63 mg/kg bm/day; USEPA, 2005d), the geometric mean of reproductive, growth, and survival NOAELs (16 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (52 mg/kg bm/day). All three of these TRVs are based on a broad set of data representing a range of species, endpoints, and exposure conditions, but there is more than an order of magnitude difference between the three TRVs, all of which are qualitatively intended to represent no to low-level effects. However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that is most consistent with only minimal to low effects on common species. Therefore, the most conservative TRV (1.63 mg/kg bm/day; USEPA 2005d) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying the selected NOAEL-based TRV and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV with a quantitatively informed level of protection.

Mercury, inorganic [Metal]

Receptor: Birds

Selected TRV = 0.8 mg/kg bm/day
Source: CEAEQ, 2012
Grade: B

Basis for the selected TRV

The selected TRV was derived by CEAEQ (2012) from a dataset of three inorganic mercury toxicity studies. CEAEQ (2012) applied Weibull dose-response methodology to calculate an EC_{20} for each of the three studies, from which CEAEQ (2012) selected what it considered to be the most appropriate EC_{20} as the TRV. The selected EC_{20} was calculated from a toxicity study (Packhurst and Thaxton, 1973; as cited in CEAEQ, 2012) in roosters exposed to inorganic mercury in drinking water for 112 days, with survival as the endpoint. The other two studies considered but not selected by CEAEQ (2012) measured a reproductive endpoint (% fertile eggs hatched) in chickens exposed to inorganic mercury in food for 42 days (Scott, 1975; as cited in CEAEQ, 2012) and short-term survival of quails after 5-day exposure to mercuric chloride in food (Hill and Soares, 1984; as cited in CCME, 1999d).

Merits of the selected TRV

The selected default TRV applied dose-response methods, which allow for the selection of a TRV with a quantified effect level. In this case, the selected TRV is based on a 20% effect level, which is consistent with the level of protection targeted for default TRVs for FCSAP (e.g., no more than minimal to low effects to common species). CEAEQ (2012) also considered studies with relevant biological endpoints (survival and reproduction) and experimental exposure conditions (e.g., exposure through diet or drinking water, for durations of 42 or 112 days), which were somewhat reflective of environmental exposure conditions.

Limitations of the recommended default TRV

Overall, there are limited toxicity data available for inorganic mercury, in contrast to organic mercury (i.e., methylmercury), which is toxicologically the most relevant form of mercury (CCME, 2000). Bird diet also plays a role in the chemical form of mercury to which wildlife is exposed (Fuchsman *et al.*, 2017). Birds that eat more from the aquatic environment will have a higher percentage of mercury exposure as methylmercury, compared to birds with a more terrestrial- and invertebrate-based diet, which typically has a lower and more variable percentage of mercury as methylmercury. Field-based measures help address uncertainties with respect to realistic environmental exposures for wildlife. These factors affecting mercury exposure are important and should be considered in ERAs on a site-specific basis. Users should consult other sources (e.g., CCME, 2000) for evaluating wildlife risks to methylmercury, as the organic form of mercury is not considered in this TRV.

Although dose-response methods were used to derive the selected TRV, only two studies were used to develop the dose-response curve. Only roosters and chickens were represented in the toxicological data underlying this TRV, and therefore, there is uncertainty in its application to other types of birds. CEAEQ (2012) applied an uncertainty factor (10) to account for using a mortality endpoint to derive this TRV.

Evaluation of candidate TRVs

Table A.40. Candidate avian toxicity reference values (TRVs) for inorganic mercury

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.019	LANL, 2014; Allaway and Stodola, 2011
0.078 [2]	USEPA Region 9 BTAG, 2009
0.8	**CEAEQ, 2012**
0.9	Sample *et al.*, 1996; Allaway and Stodola, 2011; CEAEQ, 2012; Dillon, 2013; OMOE, 2009
3.25	USEPA, 1999
1751	CCME, 1999d

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.
2. This value represents the "Unadjusted dose" (i.e., without uncertainty factors), as presented in USEPA Region 9 BTAG (2000). The USEPA Region 9 BTAG (2009) avian TRV for mercury is 0.039 mg/kg bm/day, which includes an uncertainty factor of 2 for low-effect to no-effect level conversion.

In general, there appeared to be limited data available to derive an avian TRV for inorganic mercury. Six TRVs were evaluated by FCSAP, with values ranging from 0.019 to 1751 mg/kg bm/day. One TRV (0.078 mg/kg bm/day) was not selected because it was derived from a study on organic mercury, and FCSAP's goal is to select a TRV for inorganic mercury. Two other TRVs (0.078 and 0.9 mg/kg bm/day) were screened out because they are based on LOAEL values with unknown effect sizes, so it is not clear that these TRVs are sufficiently protective to be associated with no more than minimal to low level of effects to common species. The highest TRV (1751 mg/kg bm/day) is an LC_{50} for Japanese quail and is cited in CCME (1999d) as the only wildlife toxicological study exclusively considering inorganic mercury (and not organic mercury). Ultimately, the selected TRV from CEAEQ (2012) was selected because it had several merits that the other available TRVs did not, including consideration of more than one study, utilization of dose-response methods, and quantified effect size.

Suggestions for improved future TRVs

A literature review for additional inorganic toxicity data would possibly help supplement existing datasets. Recent work in the literature on mercury TRVs (Fuchsman *et al.*, 2017) has looked at developing predictive threshold levels, which may be helpful for site-specific ERAs. These levels were not considered as candidate TRVs here, because FCSAP default TRVs are intended as more of a screening-level tool. However, the information and compilation of toxicity data as presented in Fuchsman *et al.* (2017) could be investigated further for future TRV development and may be a useful resource for site-specific ERAs. Overall, further investigation into the currently available underlying toxicological data (i.e., dose-response data) and application of recommended TRV derivation methodology (FCSAP, 2010b) could quantitatively integrate and enhance the utility of the limited toxicity data available, leading to future TRVs associated with a more quantified level of protection.

Nickel [Metal]

Receptor: Birds

Selected TRV = 6.71 mg/kg bm/day
Source: USEPA (2007b)
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset of 11 studies and is the geometric mean of eight NOAELs (four bound, four unbound) for reproduction and growth endpoints. The USEPA dataset contains toxicity data for two avian species (duck and chicken), so it is unclear whether the TRV is protective of a broader diversity of birds.

Merits of the selected TRV

Multiple toxicity studies from reliable sources were used to derive the selected TRV, and about half of the NOAEL data from these studies were bound by a LOAEL. The multi-study derivation methods mean that the selected TRV better reflects a broad range of environmental exposure conditions and receptors, as opposed to a TRV derived from a single toxicological study. In fact, the USEPA data was the only avian nickel TRV reviewed by FCSAP that utilized more than a single toxicity study in the TRV derivation process. USEPA also considered a number of relevant biological endpoints with experimental designs that typically reflect relevant environmental exposure conditions.

Limitations of the recommended default TRV

USEPA uses a NOAEL-based approach to derive TRVs, which could lead to an overly conservative TRV. The study database only considered studies on duck and chicken, so it is not representative of all avian species, but this is the case for all the TRVs evaluated for nickel on birds.

Evaluation of candidate TRVs

Table A.41. Candidate avian toxicity reference values (TRVs) for nickel

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
6.1	CEAEQ, 2012
6.71	**USEPA, 2007b; Dillon, 2013**
7	CEAEQ, 2012
9.5	Rae, 2013
22	Rae, 2013
56.3	USEPA Region 9 BTAG, 2009; Allaway and Stodola, 2011
77.4	Sample *et al.*, 1996; OMOE, 2011

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Seven TRVs were evaluated by FCSAP, with values ranging from 6.1 to 77.4 mg/kg bm/day. TRVs were screened out for a variety of reasons, such as not meeting the level of protection appropriate for a default TRV for FCSAP (7 mg/kg bm/day and 77.4 mg/kg bm/day both likely associated with greater than 25% effect) and insufficient information available to completely evaluate derivation methods (56.3 mg/kg bm/day from USEPA Region 9 BTAG, 2009).

Ultimately, the TRV of 6.71 from USEPA was selected over the TRV of 6.1 from CEAEQ (2012) because its robust derivation methods were considered by FCSAP to be superior. Although CEAEQ (2012) employs the preferred dose-response methodology, only two toxicity studies were available to develop the dose-response curve, and uncertainty factors were used. Also, CEAEQ (2012) rated its own confidence in its TRV as "low" because of the lack of data.

The remaining three TRVs are based on the USEPA dataset and represent the geometric mean of reproductive and growth NOAELs (6.71 mg/kg bm/day; USEPA, 2007b), the geometric mean of reproductive, growth, and survival NOAELs (9.5 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (22 mg/kg bm/day). All three of these TRVs are based on multiple studies and are all similar (less than a factor of three apart). However, none of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that is most consistent with only minimal to low effects on common species. Therefore, the most conservative TRV (6.71 mg/kg bm/day; USEPA, 2007b) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

A literature review for additional toxicity data would possibly help supplement existing datasets. In addition, further investigation into the currently available (e.g., USEPA dataset) underlying toxicological data (i.e., dose-response data) USEPA and application of recommended TRV derivation methodology (FCSAP, 2010b) could quantitatively integrate and enhance the utility of the limited toxicity data available, leading to future TRVs associated with a more quantified level of protection.

Supporting Scientific Rationale for FCSAP TRV

Selenium [Metalloid]

Receptor: Birds

Selected TRV = 0.29 mg/kg bm/day
Source: USEPA, 2007c
Grade: B

Basis for the selected TRV

The selected TRV was derived from an USEPA dataset of 69 avian selenium toxicity studies and is the highest bound NOAEL that is lower than the lowest bound LOAEL. The result of this derivation process was the selection of a NOAEL-based TRV from El-Begearmi and Combs (1982), who exposed avian test subjects to sodium selenite in their food for 2 weeks. The USEPA dataset included multiple bird species (duck, mallard, chicken, quail, owl, black-crowned heron and kestrel) and multiple biological endpoints (reproduction, growth and survival).

Merits of the selected TRV

The selected TRV is representative of a broad range of environmental exposure conditions and receptors because of the use of multiple toxicity studies (n=69) and avian receptors (n= 7). Biological endpoints in the dataset are relevant to population-level dynamics, and no uncertainty factors were applied in deriving the selected TRV. Additionally, the USEPA dataset was generally reflective of actual conditions because most of the underlying toxicity studies used diet as the exposure pathway, study durations were up to 105 weeks, and both organic and inorganic chemical forms of selenium were represented in the data (selenomethionine, sodium selenite, etc.).

Limitations of the recommended default TRV

The selected TRV was derived using NOAEL-based methods and may therefore be overly conservative for FCSAP purposes. However, eight LOAELs for reproduction, growth and survival from the USEPA dataset are lower than the selected TRV. Also, although the TRV from El-Begearmi and Combs (1982) is bound (they also report a LOAEL of 0.579 mg/kg bm/day), the majority (two-thirds) of the underlying toxicity studies in the USEPA dataset report unbound data. Finally, some uncertainty exists as to whether organic and inorganic selenium data are comparable when combined into the same dataset.

Evaluation of candidate TRVs

Table A.42. Candidate avian toxicity reference values (TRVs) for selenium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.23	USEPA Region 9 BTAG, 2009
0.29	**USEPA, 2007c**
0.34	CCME, 2007
0.44	Sample *et al.*, 1996 (raptors)
0.5	CEAEQ, 2012
0.5	USEPA, 1999
0.8	Sample *et al.*, 1996 (non-raptors); Allaway and Stodola, 2011; OMOE, 2011
0.85	Rae, 2013
1	Sample *et al.*, 1996 (non-raptors)
1.2	Rae, 2013
1.25	OMOE, 2011; Allaway and Stodola, 2011; Dillon, 2013
1.8	Sample *et al.*, 1996

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Twelve TRVs were evaluated by FCSAP, with values ranging from 0.23 to 1.8 mg/kg bm/day. Two TRVs were immediately screened out because insufficient information was available in the primary literature to properly evaluate their derivation methodology (0.23 mg/kg bm/day from USEPA Region 9 BTAG, 2009, and 0.34 mg/kg bm/day from CCME, 2007). Two candidate TRVs were screened out because they are LOAEL-based TRVs with unknown effect sizes, so it is unclear whether they provide a level of protection that is consistent with a minimal to low level of effects (0.8 and 1 mg/kg bm/day, both from Sample *et al.*, 1996). Five TRVs were all based on a NOAEL value from a single toxicity study (0.44 and 1.8 mg/kg bm/day from Sample *et al.*, 1996; 0.5 mg/kg bm/day from both CEAEQ, 2012, and USEPA, 1999; 1.25 mg/kg bm/day from OMOE, 2011)

The remaining three TRVs are based on the USEPA dataset and represent the highest bounded NOAEL below the lowest bounded LOAEL (0.29 mg/kg bm/day; USEPA, 2007c), the geometric mean of reproductive, growth, and survival NOAELs (0.85 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (1.2 mg/kg bm/day). All three of these TRVs are based on multiple studies and all three are similar (differing by less than a factor of 4). However, none of the three provide a quantitative measure of the level of effect they represent. So in this case, there is no clear method for selecting the TRV that provides a level of protection most consistent with no more than minimal to low level of effects. Therefore, the most conservative TRV (0.29 mg/kg bm/day; USEPA, 2007c) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

Improvements to future TRVs (both future defaults for FCSAP, as well as site-specific TRVs) may be made by a quantitative evaluation of effect sizes associated with underlying toxicological data, and application of recommended TRV derivation methodology (FCSAP, 2010b). Future TRV derivation could also include investigations into the bioaccumulation of selenium in birds (especially in birds in aquatic food webs). Other types of information (e.g., bird egg tissue residue data) may also be investigated to

further supplement and improve avian risk assessments of selenium within a weight-of-evidence approach.

Supporting Scientific Rationale for FCSAP TRV

Thallium [Metal]

Receptor: Birds

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the candidate TRVs were considered appropriate as default values for FCSAP.

Table A.43. Candidate avian toxicity reference values (TRVs) for thallium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.35	LANL, 2014; Allaway and Stodola, 2011; Dillon, 2013
0.48	Windward Environmental LLC, 2013
24	Windward Environmental LLC, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Due to limited avian thallium toxicity data, only three TRVs were available for evaluation by FCSAP at this time. The lowest TRV (0.35 mg/kg bm/day) is based on an acute LD50 value from one study (Schafer, 1972), divided by an uncertainty factor of 100 to estimate a chronic NOAEL for growth. The study was conducted on a single bird species (starling) exposed to solutions of thallium in propylene glycol by gavage. The TRV relies on an uncertainty factor to transform an acute LD50 to a chronic NOAEL; however, there is no scientific evidence to support whether the uncertainty factor can alleviate the high LD50 effect level and meet a level of protection appropriate for a default TRV for FCSAP.

The other two TRVs are both based on the same underlying toxicity study (Hudson *et al.*, 1984), where the 24 mg/kg bm/day TRV is equal to an LD50 (with no uncertainty factors applied), and the 0.48 mg/kg bm/day TRV is the LD50 divided by an uncertainty factor of 50 to approximate a NOAEL response. However, again, there is no quantitative evidence that these uncertainty factors decrease the associated magnitude of response to a level that is acceptable for a default value for FCSAP. Therefore, no TRV can be recommended for use by FCSAP as a default TRV.

Suggestions for improved future TRVs

On the basis of the criteria established for this project, none of the three available candidate TRVs were considered suitable as a FCSAP default. Future work includes sourcing additional data for thallium toxicity and investigating whether the uncertainty factor applied for thallium in LANL (2014) provides a sufficient level of protection. Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. In light of the limited toxicity data, other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments of thallium within a weight-of-evidence approach.

Uranium [Metal]

Receptor: Birds

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the evaluated TRVs were considered suitable as default values for FCSAP.

Table A.44. Candidate avian toxicity reference values (TRVs) for uranium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.04	CCME, 2007
16	Sample *et al.*, 1996; Allaway and Stodola, 2011; Dillon, 2013; CCME, 2007
78	LANL, 2014

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

The three TRVs that were evaluated ranged from 0.04 mg/kg bm/day to 78 mg/kg bm/day, and all had limitations and major concerns that precluded their selection as a default TRV for FCSAP. These limitations included limited data (a single toxicological study considered in each TRV) and concerns about the relevance of the chemical form and/or toxicological study design in deriving a default value for FCSAP.

The two higher TRVs (16 and 78 mg/kg bm/day) were both derived from the same underlying toxicological study (Haseltine and Sileo, 1983), the only difference being the application of an uncertainty factor by Sample *et al.* (1996; 16 mg/kg bm/day) to account for the short test duration (6 weeks) in Haseltine and Sileo (1983). Both of these TRVs were based on the highest tested dose level (1,600 ppm of powdered uranium in food), which was an unbound NOAEL for mortality, body mass, blood chemistry, and liver or kidney effects. Haseltine and Sileo tested the toxicity of uranium to one species, black duck, and neither Sample *et al.* (1996) nor LANL (2014) applied any allometric scaling. The two main limitations of TRVs derived from Haseltine and Sileo (1983), i.e., the elemental form of uranium to which the ducks were exposed and the unbound NOAEL endpoint, are related. The magnitude of response associated with these TRVs can be considered equal to zero because there were no significant differences between the experimental treatment groups, no trend in responses across the treatment groups, and no indication of a dose-response relationship in these data.

However, the metallic form of uranium (depleted uranium powder) used in the underlying toxicity test has low bioavailability, and therefore may be an underlying reason for the lack of observed toxic effects (Haseltine and Sileo, 1983). Because these TRVs may not be very representative of exposure conditions at federal contaminated sites, they are considered potentially under-protective for FCSAP goals.

The lowest TRV (0.04 mg/kg bm/day from CCME, 2007) provides further evidence that the higher TRVs derived from toxicity data using metallic uranium may be under-protective for FCSAP goals. The TRV from CCME (2007) was also derived from a single toxicological study (Kupsh *et al.*, 1991), which involved a one-time single exposure of quail to uranyl nitrate via injection and observed morphological changes in the birds' kidneys. The chemical form in Kupsh *et al.* (1991) is more bioavailable than metallic uranium. However, there were concerns over the study design, including experimental exposure to estrogen in addition to uranium exposure, and exposure pathway via injection, which are not representative of exposure conditions at federal contaminated sites. The magnitude of response associated with the bound NOAEL from Kupsh *et al.* (1991) could not be readily calculated because the kidney lesion endpoints were categorical ("no lesions", "mild", "moderate", "severe"), rather than continuous.

The available TRVs spanned four orders of magnitude, considered only two avian species (mallard or quail), and had major concerns regarding relevance of toxicological data to FCSAP goals, which prevented selection of a default recommended TRV for FCSAP at this time.

Suggestions for improved future TRVs

On the basis of the criteria established for this project, none of the available candidate TRVs were considered suitable for FCSAP. Further investigation is recommended to develop a default TRV that is appropriate for FCSAP, given the high degree of uncertainty and limitations associated with the available TRVs and the overall limited amount of toxicity data for avian uranium toxicity. Future steps should include performing a search for any new or updated toxicity data and applying recommended TRV derivation methods (FCSAP, 2010b; e.g., dose-response based approach) to enhance the utility of the limited toxicity data available. Future TRV development could also consider additional types of data where available, such as tissue-residue data regarding uranium toxicity, within a weight-of-evidence approach.

Vanadium [Metal]

Receptor: Birds

Selected TRV = 0.344 mg/kg bm/day
Source: USEPA, 2005e
Grade: B

Basis for the selected TRV

The selected TRV is from USEPA (2005e) and is the highest bound NOAEL that is lower than the lowest bound LOAEL for reproductive, growth, and survival endpoints from 36 vanadium toxicity studies on birds. The resulting TRV from USEPA (2005e) comes from a study by Hill (1979), who exposed juvenile female chickens (*Gallus domesticus*) to vanadium for 5 weeks through their diets and evaluated subsequent effects on a growth endpoint. Because 36 studies were incorporated into the derivation process, this TRV is considered to be representative of multiple bird species (chicken, duck and Japanese quail) using relevant biological endpoints (survival, growth and reproduction).

Merits of the selected TRV

Derivation of the selected TRV considered many different toxicological studies (n=36) and multiple relevant biological endpoints (reproduction, growth, and survival) and did not employ uncertainty factors. Because the TRV is based on a NOAEL (for growth), it likely provides a level of protection that is consistent with a minimal to low level of effects. The exposure durations of the toxicity tests included in the USEPA (2005e) dataset for deriving a TRV were up to 84 days. Exposure pathways were dietary, and chemical forms of vanadium included ammonium metavanadate, sodium metavanadate, calcium vanadate, vanadyl sulfate and vanadate chloride.

Limitations of the recommended default TRV

Avian vanadium toxicity data are only available for a few species of birds (chicken, duck, and Japanese quail), with a strong reliance on chicken data. Therefore, the TRV is potentially limited in terms of its application to all avian species. The study uses NOAEL-based derivation methods, which is generally not recommended for TRV derivation by FCSAP. As well, the effect size is uncertain, so there is a possibility that the TRV is overly conservative.

Evaluation of candidate TRVs

Table A.45. Candidate avian toxicity reference values (TRVs) for vanadium

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.344	**USEPA, 2005e; Dillon, 2013**
0.57	OMOE, 2011; Allaway and Stodola, 2011
1.9	Rae, 2013
2.0	Rae, 2013
11.4	Sample *et al.*, 1996

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Five TRVs were evaluated by FCSAP, ranging in value from 0.344 to 11.4 mg/kg bm/day. The OMOE (2011) TRV of 0.57 mg/kg bm/day was screened out because insufficient information was available to

fully evaluate derivation methods, as only an abstract was available for the underlying toxicological study. The highest TRV (11.5 mg/kg bm/day; Sample *et al.*, 1996) was based on an unbound NOAEL for survival, growth and blood chemistry from a single study and did not involve any uncertainty factors or allometric scaling. However, it was not selected because the USEPA TRV considered a broader range of data (132 data points from 36 studies). The robust dataset used for the USEPA TRV supported its selection as a default value for FCSAP.

There were two other TRVs (from Rae, 2013) that were also based on a subset of the toxicological data in the USEPA dataset: 1.9 and 2.0 mg/kg bm/day, based on the geometric mean of the reproductive, growth, and survival NOAELs and LOAELs, respectively. However, none of the three TRVs based on the USEPA dataset provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that best quantitatively provides a level of protection that is consistent with a minimal to low level of effects. Therefore, the most conservative TRV (0.344 mg/kg bm/day; USEPA, 2005e) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

A more quantitative investigation into the dose-response data from the toxicological studies in the USEPA dataset and application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) will potentially lead to improved TRVs in the future. For example, calculation of the effect sizes associated with available underlying toxicological data could improve future TRV derivations.

Zinc [Metal]

Receptor: Birds

Selected TRV = 66.1 mg/kg bm/day
Source: USEPA, 2007e
Grade: B

Basis for the selected TRV

The selected TRV is from an USEPA dataset (2007e) and is the geometric mean of 43 NOAELs for reproduction or growth. Roughly half of these NOAELs were bound, and the other half were unbound. The dataset includes toxicity tests conducted on a variety of avian species (chicken, duck, turkey, and quail), and typically involved exposing test animals to zinc through food.

Merits of the selected TRV

The selected TRV considers a broad set of data, representing a variety of exposure conditions (e.g., laboratory test duration and design), and avian species (chicken, duck, turkey, and quail). Biological endpoints used to calculate this TRV (reproduction and growth) are relevant to population-level dynamics and no uncertainty factors were applied in deriving the selected TRV. Additionally, the USEPA dataset was generally reflective of environmental conditions because all of the underlying toxicity studies used diet as the exposure pathway, and study durations were up to 44 weeks long (308 days).

Limitations of the recommended default TRV

USEPA (2007e) used a NOAEL-based approach to derive this selected TRV, which may mean that this TRV is overly conservative for FCSAP objectives. However, in the USEPA dataset, there are five unbound LOAELs (one for reproduction, and four for growth) that are below the selected TRV, which demonstrates the possibility that adverse effects may still occur below the selected TRV. Overall, the range in values for NOAELs and for LOAELs in the USEPA (2007e) dataset is broad, spanning almost two order of magnitude. For example, reproductive, growth, and survival NOAELs range between 13.8 and 741.8 mg/kg bm/day, and that of LOAELs ranges between 21.6 and 1370 mg/kg bm/day. Therefore, it is hard to assign a quantitative level of protection provided by this TRV.

Evaluation of candidate TRVs

Table A.46. Candidate avian toxicity reference values (TRVs) for zinc

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
17.2	USEPA Region 9 BTAG, 2009
66.1	**USEPA, 2007e; Dillon, 2013**
83	Rae, 2013
130.9	CEAEQ, 2012
131	Sample *et al.*, 1996; Allaway and Stodola, 2011; OMOE, 2011
190	Rae, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Six avian zinc TRVs, ranging from 17.2 to 194 mg/kg bm/day, were evaluated by FCSAP. The lowest TRV (from USEPA Region 9 BTAG, 2009) was screened out because insufficient information was available in the primary literature to effectively evaluate derivation methods. The EC_{20} TRV from CEAEQ (2012; 130.9) was screened out because although they employed Weibull statistical methods to develop a dose-response curve for individual studies, only one acute toxicity study was used as the underlying data for the curve. Therefore, this TRV has uncertain relevance to a broad range of species, endpoints, or exposure conditions. The TRV from Sample *et al.* (1996; 131 mg/kg bm/day) was based on a bound reproductive LOAEL (egg hatchability) for white leghorn hen from a single toxicological study. This LOAEL was associated with a 20% effect level, which meets a level of protection appropriate for a default TRV for FCSAP. However, it still shares the same limitations as all TRVs based on only a single study, most importantly being that it is hard to quantify how this TRV fits into the distribution of toxicological responses across a range of species, endpoints, and exposure conditions.

The remaining three TRVs are based on the USEPA dataset and represent the geometric mean of reproductive and growth NOAELs (66.1 mg/kg bm/day; USEPA, 2007e), the geometric mean of reproductive, growth, and survival NOAELs (83 mg/kg bm/day), and the geometric mean of reproductive, growth, and survival LOAELs (190 mg/kg bm/day). None of the three provide a quantitative measure of the level of effect that they represent. So in this case, there is no clear method for selecting the TRV that is most consistent with only minimal to low effects on common species. Therefore, the most conservative of these three TRVs (66.1 mg/kg bm/day; USEPA, 2007e) was selected as a default TRV for FCSAP.

Suggestions for improved future TRVs

In the future, improved TRVs that are more aligned with FCSAP TRV guidance (FCSAP, 2010b) and have a more quantified level of protection may be developed. Although somewhat effort-intensive, this would involve calculating the effect size and dose-response data associated with the study(ies) underlying the selected NOAEL-based TRV and then applying dose-response methodology (FCSAP, 2010b) to derive a new TRV with a quantitatively informed level of protection.

Anthracene [LMW PAH]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian anthracene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Fluorene [LMW PAH]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian fluorene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Naphthalene [LMW PAH]

Receptor: Birds

Selected TRV = 7.7 mg/kg bm/day
Source: Klasing, 2007
Grade: C

Basis for the selected TRV

The selected TRV is based on one toxicity study (Klasing, 2007) that reported a NOAEL for growth in Japanese quail, from exposure to naphthalene in the diet for 14 weeks. Although this NOAEL was not statistically different from the experiment's control, this treatment level was still associated with 20% decreased growth relative to control during weeks 6 to 14 of the experiment. Final body mass after 14 weeks was not very different from the control (NOAEL treatment level = 131 g; control group = 132 g). The corresponding LOAEL from Klasing (2007) was 31.5 mg/kg bm/day.

Merits of the selected TRV

No allometric or uncertainty factors were used, and the study design is generally reflective of actual conditions because it exposed test animals (quail) to a LMW PAH (naphthalene) through diet. Furthermore, data available in the underlying toxicity study (Klasing, 2007) allows calculation of an effect size.

Limitations of the recommended default TRV

This TRV is based on only a single study, and therefore, there is limited information available at this time to evaluate the selected TRV (based on a single toxicological study) within the context of a broader range of information about a variety of species, endpoints, or exposure conditions as is relevant for FCSAP goals.

Evaluation of candidate TRVs

Table A.47. Candidate avian toxicity reference values (TRVs) for naphthalene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
7.7	**Klasing, 2007**
15	LANL, 2014; Allaway and Stodola, 2011; Dillon, 2013

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Only two avian TRVs for naphthalene were identified for evaluation as candidate default FCSAP TRVs. The higher TRV (15 mg/kg bm/day) is an unbound NOAEL from LANL (2014) and is based on a toxicity study by W. R. Landis Assoc., Inc. (1985) in which Bobwhite quail were exposed to naphthalene through their diets at concentrations of 0, 316, 562, 1,000, 1,780, 3,160, and 5,620 ppm for 5 days. The biological endpoint was juvenile mortality, which represents survival of a critical life stage. The NOAEL was divided by an uncertainty factor of 100 to account for the short duration of the toxicity test, which is typically not recommended unless justified by clear scientific rationale.

Although both of the available TRVs shared some merits (e.g., relevant endpoint, exposure to naphthalene through food), and some limitations (e.g., based on a single study), the lower TRV (7.7

mg/kg bm/day; Klasing, 2007) was selected because it reported a quantitative effect size (20% reduced growth in quail, although this effect level was not significantly different from the study's control) that was likely to provide a sufficient level of protection, did not apply uncertainty factors, and studied the quails response over a longer exposure duration (14 weeks).

Suggestions for improved future TRVs

Future work may include sourcing additional data for naphthalene toxicity. Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology (e.g., Hill *et al.*, 2014) that can enhance the utility of limited existing toxicological information across different studies, species, and endpoints. In light of the limited toxicity data, other types of information may also be incorporated in a weight-of-evidence approach to risk assessments.

Phenanthrene [LMW PAH]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian phenanthrene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Supporting Scientific Rationale for FCSAP TRV Evaluation

Low Molecular Weight Polycyclic Aromatic Hydrocarbons [LMW PAHs]

Receptor: Birds

Selected TRV = 7.7 mg/kg bm/day
Source: Parametrix *et al.*, 2010
Grade: C

Basis for the selected TRV

The selected TRV was applied to LMW PAHs by Parametrix *et al.* (2010) in a screening level risk assessment at the Upper Columbia River. This TRV is based on one toxicity study (Klasing, 2007) that reported a NOAEL for growth in Japanese quail, from exposure to naphthalene in the diet for 14 weeks. Although this NOAEL was not statistically different from the experiment's control, this treatment level was associated with 20% decreased growth relative to control during weeks 6 to 14 of the experiment. Final body mass after 14 weeks was not very different from the control (NOAEL treatment level = 131 g; control group = 132 g). The corresponding LOAEL from Klasing (2007) was 31.5 mg/kg bm/day.

Merits of the selected TRV

No allometric or uncertainty factors were used, and the study design is generally reflective of actual conditions because it exposed test animals (quail) to a LMW PAH (naphthalene) through diet. Furthermore, data available in the underlying toxicity study (Klasing, 2007) allows calculation of an effect size.

Limitations of the recommended default TRV

This TRV is based on only a single study, and therefore, there is limited information available at this time to evaluate the selected TRV (based on a single toxicological study) within the context of a broader range of information about a variety of species, endpoints, or exposure conditions as is relevant for FCSAP goals. This TRV is also only based on data for one chemical (naphthalene), while being applied to a broad set of LMW PAHs.

Evaluation of candidate TRVs

Table A.48. Candidate avian toxicity reference values (TRVs) for LMW PAHs

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
7.7	**Parametrix *et al.*, 2010**

The selected TRV has its limitations (described above), however it was the only TRV available to apply to LMW PAHs (as a sum of individual LMW PAHs), and may be used as a default value for FCSAP.

Suggestions for improved future TRVs

Future work may include sourcing additional data for toxicity of LMW PAHs (both naphthalene and other LMW PAHs). Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b), particularly dose-response methodology (e.g., Hill *et al.*, 2014) that can enhance the utility of existing limited toxicological information across

different studies, species, and endpoints. In light of the limited toxicity data, other types of information may also be incorporated in a weight-of-evidence approach to ecological risk assessments.

Benz(a)anthracene [HMW PAH]

Receptor: Birds

Selected TRV = 0.107 mg/kg bm/day
Source: LANL, 2014
Grade: C

Basis for the selected TRV

The selected TRV originates from LANL (2014) and is based on a toxicological study by Beall (2007). The TRV is a subchronic, unbound NOAEL from a study by Beall (2007), in which Bobwhite quail were exposed to test doses of 0, 1, 10, 100 and 1000 mg/kg through food consumption and measured survival, reproduction and growth effects. An uncertainty factor of 10 was applied to correct for the subchronic duration of the study.

Merits of the selected TRV

LANL (2014) methodology utilized acceptable biological endpoints by looking at growth (adverse effects on ability of individuals to develop into viable organisms), reproduction (successful breeding and ability to produce live and equally viable offspring), and survival. Also, the dietary exposure pathway is considered reflective of field conditions.

Limitations of the recommended default TRV

Limitations of the selected TRV include that it is based on a single study that conducted an experiment on one species, Bobwhite quail. The study was also done for a short duration exposure (sub chronic-NOAEL), and uncertainty factors were therefore applied to transform it into a chronic NOAEL. The practice of applying uncertainty factors to correct for issues with experimental design is generally not recommended by FCSAP. Finally, because the TRV is a NOAEL, and no effects were observed for survival, growth, or reproduction endpoints at any of the tested dose-levels in Beall (2007), this TRV may be overly conservative for FCSAP purposes.

Evaluation of candidate TRVs

Table A.49. Candidate avian toxicity reference values (TRVs) for benz(a)anthracene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
0.0079	Brunstrom *et al.*, 1991
0.079	USEPA, 1999
0.107	**LANL, 2014; Allaway and Stodola, 2011; Dillon, 2013**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

Three TRVs for birds were evaluated for benzo(a)anthracene. Although the selected TRV has several limitations (described above), there were significant concerns that the level of effect associated with each of the other two available TRVs (0.0079 and 0.079 mg/kg bm/day), both based on the same underlying toxicological study (Brunstrom *et al.*, 1991), may be too severe for the level of protection appropriate for a default TRV for FCSAP. Both of these TRVs were based on an LD50 for chick embryos (White leghorn or Shaver chickens) in eggs injected one time with benz(a)anthracene. Injection-based exposures are not considered a relevant exposure pathway because they do not account for gastric

bioavailability (Hill *et al.*, 2014), and therefore it is difficult to make direct numerical comparisons between the two TRVs based on injection experimental exposures (Brunstrom *et al.*, 1991; USEPA, 1999), and the one TRV based on dietary exposure (LANL, 2014). There was no uncertainty factor applied in the 0.079 mg/kg bm/day TRV. USEPA (1999) applied an uncertainty factor of 0.01 to compensate for the acute exposure duration in the underlying toxicity test.

Suggestions for improved future TRVs

Derivation of a new TRV is recommended. Future work may include sourcing additional data for benzo(a)anthracene toxicity. Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. In light of the limited toxicity data, other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments of benzo(a)anthracene within a weight-of-evidence approach.

Benzo(a)pyrene [HMW PAH]

Receptor: Birds

Selected TRV = 0.001 mg/kg bm/day
Source: USEPA, 1999
Grade: C

Basis for the selected TRV

The selected TRV is from USEPA (1999) and is based on a bound reproductive NOAEL (egg mortality) from Brunstrom *et al.* (1991). In the underlying experiment, chicken eggs were injected one time with benzo(a)pyrene dissolved in peanut oil. The TRV was derived by dividing the NOAEL dose level (0.1 mg/kg egg) by an uncertainty factor of 100 to correct for the acute (one-time) exposure. One other dose level was tested in Brunstrom *et al.* (1991), the LOAEL dose level (0.3 mg/kg egg), which was associated with 55% mortality in the chicken eggs.

Merits of the selected TRV

This TRV is based on a relevant endpoint (survival in eggs).

Limitations of the recommended default TRV

This TRV has several limitations. The application of the uncertainty factor (0.01) has unknown implications for the quantitative level of protection provided by this TRV. The injection exposure pathway (injection) is not representative of realistic environmental exposure pathways. Moreover, this TRV is predicated on the assumption that a dose in units of mg/kg egg is directly equal to a dose in mg/kg bm/day in birds at all life stages, and it is based on toxicity data for a single species (chicken) and single life stage (egg) only, with no information on toxicity at chick or adult life stages. In addition, this TRV considers a single study, which is likely not very representative of a range realistic exposure conditions.

Evaluation of candidate TRVs

Table A.50. Candidate avian toxicity reference values (TRVs) for benzo(a)pyrene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
0.001	**USEPA, 1999**
0.1	Brunstrom *et al.*, 1991
1.43	Hough *et al.*, 1993

Three TRVs for birds were evaluated for benzo(a)pyrene. Although the selected TRV has several limitations (described above), there were significant concerns that the level of effect associated with each of the other two available TRVs (0.1 and 1.43 mg/kg bm/day) may be too severe to be applied as a default value for FCSAP. The 0.1 mg/kg bm/day TRV was based on the same study as the selected TRV, except that there were no uncertainty factors applied to this TRV. The original paper also reported that all 20 chick embryos in the 0.1 mg/kg egg treatment group survived for 72 hours (equivalent to 0% effect for this endpoint). However, chick embryo survival was more than halved in the other experimental dose level (0.3 mg/kg egg), with only 9 of 20 chick embryos surviving after 72 hours. The two dose levels tested in Brunstrom *et al.* (1991) are fairly close together, and in the absence of additional data from other toxicological studies, it is difficult to ascertain whether or not a

TRV of 0.1 mg/kg bm/day would be protective of a variety of species, endpoints, and relevant exposure conditions to a level that allows no more than minimal to low level of effects.

The TRV from Hough *et al.* (1993) is based on a 100% effect level, at which complete infertility was reported for female pigeons exposed to 10 mg/kg bm/week (equivalent to 1.43 mg/kg bm/day) via weekly injections of benzo(a)pyrene in corn oil, for 3 to 6 months. The magnitude of effect associated with 1.43 mg/kg bm/day is too severe to be applied as a default for FCSAP.

Suggestions for improved future TRVs

Derivation of a new TRV is recommended. Future work may include sourcing additional data for benzo(a)pyrene toxicity. Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. In light of the limited toxicity data, other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments of benzo(a)pyrene within a weight-of-evidence approach.

Pyrene [HMW PAH]

Receptor: Birds

Selected TRV = 20.5 mg/kg bm/day
Source: LANL, 2014
Grade: C

Basis for the selected TRV

Limited avian pyrene toxicity data is available, and only one TRV (LANL, 2014) was evaluated by FCSAP. The TRV is an unbound NOAEL from Beall (2007), in which Bobwhite quail are exposed to a single dose of pyrene (2,000 mg/kg) through gavage and observed for 2 days to determine a mortality effect. An uncertainty factor of 100 was applied to the TRV to account for the short exposure time and make it more reflective of chronic exposure conditions.

Merits of the selected TRV

No allometric scaling was used in TRV derivation, and the biological endpoint used (mortality) is relevant to population-level dynamics.

Limitations of the recommended default TRV

Because the selected TRV is derived from a single toxicity study in only one species of bird, its applicability as a TRV for all avian species is debatable. The test subjects were exposed to a single dose of pyrene, which means the data are an unbound NOAEL and do not provide a comprehensive picture of the dose-response relationship. NOAEL data can also be overly conservative for FCSAP purposes. The study duration is very short (2 days), and although this was corrected for using an uncertainty factor, the selection of uncertainty factors is arbitrary and therefore not recommended for use in TRV derivation by FCSAP. Finally, gavage is not an exposure route that is reflective of actual conditions in the environment.

Evaluation of candidate TRVs

Table A.51. Candidate avian toxicity reference values (TRVs) for pyrene

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
20.5	**LANL, 2014; Allaway and Stodola, 2011; Dillon, 2013**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

The selected TRV has many limitations that do not adhere to FCSAP guidance for TRV derivation. However, given the lack of an available substitute at this time, the TRV can be applied as a default TRV for FCSAP, with consideration given to its substantial limitations, particularly where risk may be driven by this contaminant.

Suggestions for improved future TRVs

The selected default TRV is based on an unbound NOAEL, which is generally not recommended by FCSAP (2010b) for derivation of TRVs, as it indicates that none of the doses tested in the study showed an effect and thus the threshold for the effect is unknown. This TRV may therefore be overly conservative for FCSAP sites. Furthermore, there are no additional data available that can be used to

put these TRVs into a broader context for multiple species, endpoints, or ecologically relevant exposure conditions. To improve future effects assessments, updated literature searches for additional toxicology data may help supplement the currently limited set of available data. Future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. Other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments of hexavalent chromium within a weight-of-evidence approach.

High Molecular Weight Polycyclic Aromatic Hydrocarbons [HMW PAHs]

Receptor: Birds

Selected TRV = None Suitable
Source: None Suitable
Grade: None Suitable

Basis for the selected TRV
None Suitable

Merits of the selected TRV
None Suitable

Limitations of the recommended default TRV
None Suitable

Evaluation of candidate TRVs
None of the candidate TRVs were considered appropriate as default values for FCSAP.

Table A.52. Candidate avian toxicity reference values (TRVs) for HMW PAHs

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
0.00014	USEPA, 1999
1.43	Parametrix *et al.*, 2010

Neither of the available avian TRVs for HMW PAHs were considered suitable for FCSAP primarily because of the severity of their associated effect size and because the environmental relevance of the exposure pathways in the underlying toxicity data is uncertain. The lower TRV (0.00014 mg/kg bm/day; USEPA, 1999) was based on an LD50 for chicken embryos injected with benzo(k)fluoranthene (reported in Brunstrom *et al.*, 1991) divided by an uncertainty factor of 100. The higher TRV (1.43 mg/kg bm/day; Parametrix *et al.*, 2010) was associated with complete infertility in female pigeons exposed to benzo(a)pyrene in corn oil via weekly injections for 3 to 6 months. Therefore, this TRV is associated with a 100% effect to a reproductive endpoint, which is too severe for the level of protection appropriate for a default TRV for FCSAP. Both TRVs are based on a single study, and therefore there is limited information available at this time to evaluate the available TRVs within the context of a broader range of information about a variety of species, endpoints, or exposure conditions, as is relevant for FCSAP goals, or about a range of different HMW PAHs.

Suggestions for improved future TRVs
On the basis of the criteria established for this project, none of the available candidate TRVs were considered appropriate or sufficient for FCSAP. Derivation of a new TRV is recommended. Future work should involve a thorough literature review to source new data that will allow for the derivation of a new TRV that incorporates a broader context of toxicity information. Future avian TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b), particularly dose-response methodology (e.g., Hill *et al.*, 2013) that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints.

In light of the limited toxicity data, other types of information may also be incorporated in a weight-of-evidence approach to risk assessments.

Benzene [Volatile Organic]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian benzene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Ethylbenzene [Volatile Organic]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian ethylbenzene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Toluene [Volatile Organic]

Receptor: Birds

Selected TRV = None Available
Source: None Available
Grade: None Available

No avian toluene toxicity data is available at this time. Therefore, no TRVs have been evaluated by FCSAP. Future work should include a thorough literature search to find relevant toxicity data which can be used to derive a new default TRV for FCSAP. Derivation of any new TRVs (either default values or site-specific) should apply recommended methodology for TRV derivation (FCSAP, 2010b) to existing and any potential new toxicological data and/or include additional lines of evidence to inform effects assessments within a broader weight-of-evidence approach.

Xylenes [Volatile Organic]

Receptor: Birds

Selected TRV = 107 mg/kg bm/day
Source: LANL, 2014
Grade: C

Basis for the selected TRV

The only available avian xylenes TRV is from LANL (2014) and is an unbound NOAEL value from an acute toxicity study by Hill and Camardese (1986) with mortality as the biological endpoint. Japanese quail were exposed to xylenes through their diet for 5 days, at a concentration of 10,667 mg/kg bm/day. An uncertainty factor of 10 was applied to account for the acute duration of exposure.

Merits of the selected TRV

The TRV is a NOAEL, so it is considered to provide a sufficient level of protection as a default for FCSAP (although potentially overly conservative). No allometric scaling was used, and the TRV was derived using an appropriate biological endpoint (mortality). Generally, the experimental design was found to reflect actual conditions in the environment (with some exceptions described below) because the chemical form was 100% xylenes (reagent grade), which was administered through dietary exposure.

Limitations of the recommended default TRV

Because the selected TRV is based on a single toxicity study in only one species of bird, its applicability to all avian species is uncertain. The value employed is an unbound acute NOAEL, which does not provide a comprehensive picture of the dose-response relationship. As well, an uncertainty factor has been applied to account for the acute study duration, and the selection of uncertainty factors is generally an arbitrary process with no grounding in scientific fact. Finally, the evaporation rate of xylenes (a volatile substance) was not accounted for in the experimental design, so the actual exposure of the test subjects to xylenes may have been much lower than that reported in the study.

Evaluation of candidate TRVs

Table A.53. Candidate avian toxicity reference values (TRVs) for xylenes

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)[1]
107	**LANL, 2014; Allaway and Stodola, 2011; Dillon, 2013**

1. The first-listed source is the main citation where the candidate TRV was first published. Subsequent listed sources have also selected or cited that candidate TRV, but did not derive the candidate TRV themselves.

The selected TRV has its limitations (as described above), but given the limited avian toxicity data available for xylene and the lack of an appropriate substitute, the selected TRV may be used as a default value for FCSAP. Consideration should, however, be given to its substantial limitations, especially where risk at a site is being driven by this contaminant.

Suggestions for improved future TRVs

The selected default TRV is based on an unbound NOAEL, which is generally not recommended by FCSAP (2010b) for developing TRVs, because they represent toxicity tests in which no adverse effects were observed at any of the tested dose levels. This TRV may therefore be overly conservative for FCSAP sites. Furthermore, there are no additional data available that can be used to put these TRVs into a broader context for multiple species, endpoints, or ecologically relevant exposure conditions. To improve future effects assessments of xylenes in birds, updated literature searches for additional toxicology data may help supplement the currently very limited set of available data. Future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2), particularly dose-response methodology that can enhance the utility of existing and any additional toxicological information across different studies, species, and endpoints. Other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve avian risk assessments within a weight-of-evidence approach.

Petroleum Hydrocarbons [PHCs]

Receptor: Birds

Selected TRV = 125 mg/kg bm/day (Total PHCs)
Source: Szaro (1977)
Grade: C

Basis for the selected TRV

The selected TRV is derived from a primary toxicological study by Szaro (1977), in which 50 juvenile mallard ducklings were exposed to crude oil in the diet for an 8-week period (56 days). This TRV is based on a NOAEL for increased liver weight relative to control, which was the most sensitive of all the endpoints measured in Szaro (1977; other reported endpoints included body mass, and spleen weight). This TRV is calculated assuming that the concentrations reported in Szaro (1977) in parts per million (ppm) of crude oil in the diet are reported on a dry mass basis (as opposed to a liquid volumetric basis). Furthermore, diet concentrations in Szaro (1977) were converted from ppm crude oil in the diet to units of mg/kg bm/day by multiplying the diet concentration (in ppm) by food ingestion rate for mallards (0.05 kg/bm/day; FCSAP, 2012b). Treatment levels reported in Szaro (1977) were 250 ppm; 2,500 ppm; 25,000 ppm; and 50,000 ppm crude oil in the diet, with the selected TRV of 125 mg/kg bm/day calculated from the 2,500 ppm treatment level.

Merits of the selected TRV

The underlying toxicological study exposed birds to PHCs in food, which is likely similar to how birds would be exposed to PHCs in environmental situations. Juvenile mallard ducks were exposed to PHCs through food contaminated with crude oil product. No allometric scaling or uncertainty factors were used in the derivation of this TRV, thereby limiting uncertainties related to this TRV.

Limitations of the recommended default TRV

This TRV was based on a single study with a single avian species. Therefore, it is not possible to quantify uncertainty associated with this TRV in terms of natural range in biological responses to PHC exposure between different types of birds. There is uncertainty in extrapolating an effect from a single study, to assessing any possible population-level effects in an ERA. The endpoint on which this TRV is based, i.e., change in liver weight, has uncertain relevance to survival, reproduction, and growth endpoints, which are typically preferred for wildlife TRVs used in ERAs. This TRV is based on a NOAEL, which is less preferred to TRVs with a quantified effect level. There is also some level of uncertainty in selecting a TRV from a toxicity study in which the dose levels were based on a logarithmic scale; the experimental treatment levels above and below the selected TRV were 0.025% and 2.5% crude oil in the diet (or 12.5 and 1,250 mg/kg bm/day). There is also uncertainty in terms of how well this TRV may apply to different types of PHCs with varying compositions; lighter PHC mixtures are typically considered more toxic than heavier PHC mixtures.

Evaluation of candidate TRVs

Table A.54. Candidate avian toxicity reference values (TRVs) for total petroleum hydrocarbons (PHCs)

Candidate TRV (mg/kg bm/day)	Source (See Reference Section 3)
40	Patton and Dieter (1980)
125	**Szaro (1977)**
1250	Szaro (1977)
2500	Szaro (1977)
2990)	Harvey *et al.* (1982)

Five avian TRVs for PHCs were evaluated as candidate default FCSAP TRVs. The lowest TRV (40 mg/kg bm/day; Patton and Dieter, 1980) is based on a NOAEL for mallard growth exposed to a PAH/PHC mixture in food. However, it was not selected as a default for FCSAP because of uncertain confounding variables in the underlying toxicological study, including weight loss within the duration of the study, which was attributed to food avoidance rather than toxic effects of PHC exposure.

The highest TRV (2,990 mg/kg bm/day; Harvey *et al.*, 1982) is based on a reproductive LOAEL (endpoint was egg laying rate) for mallards exposed to crude oil in their diet over a 30-week exposure period. However, that TRV was not selected as a default for FCSAP because it was associated with a 90% to 95% reduction in the test animal's egg laying rate, which is considered too severe to protect to a level of no more than minimal to low level of effects. Furthermore, there were other limitations associated with the underlying toxicological study design that had uncertain implications for TRV development.

The remaining three TRVs were based on the same toxicological study, Szaro (1977), which is also cited in Appendix VI of CCME (2010). Each of these three TRVs represents experimental treatment levels (i.e., NOAELs/LOAELs for various endpoints). The highest of the three TRVs, reported as 50,000 ppm (or 5%) crude oil in the diet in Szaro (1977) and calculated as 2,500 mg/kg bm/day (using an ingestion rate of 0.05 kg/bm/day from FCSAP, 2012b) represents the LOAEL for body mass. Significant effects relative to control on liver and spleen weights were also noted at this treatment level. This value was not selected as a FCSAP default because, although it was derived from a LOAEL for growth endpoint that was associated with an 18% effect level, there was evidence in the underlying toxicological data that this dose level may be associated with effect levels for other relevant endpoints (i.e., reproductive endpoints) that were considered too severe to provide level of protection consistent with no more than minimal to low level of effects. Furthermore, Szaro (1977) noted retarded feather development at this high dosage level, which may have relevance at a population or individual animal level within a site-specific ERA. The 1,250 mg/kg bm/day TRV from Szaro (1977) is from the 25,000 ppm (or 2.5%) treatment level and represents the experiment's NOAEL for body mass, as well as the LOAEL for liver and spleen weights. The lowest of these three TRVs, reported as 2,500 ppm (or 0.25%) crude oil in the diet in Szaro (1977) and calculated as 125 mg/kg bm/day, was the NOAEL for all endpoints and was conservatively selected as the default TRV for FCSAP as described above. All three of these TRVs from Szaro (1977) share several uncertainties and assumptions in their interpretation. For one, the TRVs from Szaro (1977) are reported here assuming that the concentrations presented in Szaro (1977) in units of ppm of crude oil in the diet are on a dry mass basis. The ppm units may also be interpreted on a liquid volumetric basis, in which case the density of crude oil would need to be incorporated into the conversion from units of ppm to mg/kg bm/day. Secondly, these TRVs are calculated with an ingestion rate that uses the average body mass of an adult duck (as per FCSAP, 2012b), while the toxicity test

was conducted on juveniles. In cases where juveniles are exposed as the test animals, it is a challenge to use dose as the metric of exposure because their body mass is changing, and it may be preferable to use concentration in food. All three of the TRVs from Szaro (1977) also share some merits in that they are based on toxicity data for crude oil, a complex mixture of contaminants, and can therefore be used to assess risks associated with total PHC exposure concentrations in an ERA.

Suggestions for improved future TRVs

It is recognized that there are generally limited data available for deriving bulk hydrocarbon TRVs for wildlife, as noted by CCME (2008). To improve future effects assessments, updated literature searches for additional toxicology data may help supplement the currently limited set of available data so as to be able to put these TRVs into a broader context for multiple species, endpoints, and ecologically relevant exposure conditions. Future TRV development would also benefit from application of FCSAP's recommended TRV derivation methodology (ERA guidance document, Module 2). Given the limitations of available toxicology data and the uncertainties and complexities associated with complex PHC mixtures, other types of information (e.g., tissue residue data) may also be investigated to further supplement and improve risk assessments within a weight-of-evidence approach.

Polychlorinated Biphenyls [PCBs]

Receptor: Birds

Selected TRV =2.3 ng TEQ/kg bm/day
Source: CCME, 2001a
Grade: C

Basis for the selected TRV

This TRV is also the basis for the current Canadian Tissue Residue Guideline for the Protection of Wildlife Consumers of Aquatic Biota (CCME, 2001a). Complete details on the derivation of this value are provided in CCME (2001a). It should be noted that the TRV for PCBs is expressed in **units of ng toxic equivalency units (TEQs)/kg bm/day**. This TRV is based on the geometric mean of the NOAEL and LOAEL for growth in white leghorn chicks of hens fed PCBs in the diet (Lillie *et al.*, 1974). The study by Lillie *et al.* (1974) was selected as the basis for the CCME (2001a) tissue residue guideline because it was the most sensitive study from a set of relevant studies. CCME (2001a) also noted that white leghorn chicks may be inherently 10 to 1,000 times more sensitive to exposure than other avian species (e.g., raptors). This TRV is therefore likely to be protective of a broad set of avian species that may be present on federal contaminated sites.

Merits of the selected TRV

The toxicological study was selected from a set of studies that included a range of species (e.g., chicken, pheasants, kestrel, and quail) and is therefore likely to be protective of a range of avian species on federal contaminated sites. No uncertainty factors were applied to account for differences in interspecies sensitivities. This TRV is also based on a relevant reproductive endpoint (growth of offspring from adults exposed to PCBs in the diet). As a unique issue to PCB TRVs, this value applied toxic equivalency factors (TEFs), as recommended by the World Health Organization (van den Berg *et al.*, 1998), so that toxicities of PCB mixtures with different PCB congener compositions could be directly compared (see CCME 2001a for a description of TEFs and how they were applied in this TRV).

Limitations of the recommended default TRV

The magnitude of effect associated with this TRV is not quantified because the TRV was derived as the geometric mean of a NOAEL and LOAEL value. The LOAEL used in the geometric mean behind this selected TRV was associated with a 10% reduction in chick growth, which is sufficient to provide a level of protection that is consistent with no more than minimal to low level of effects. The NOAEL that was used in geometric mean behind this TRV was calculated as this LOAEL divided by 5.6. Therefore, there is uncertainty behind the magnitude of effect associated with this TRV. Given the complexity of trying to characterize the effects of complex mixtures, this TRV is focused on toxicity of coplanar PCB congeners, which share a similar mode of action (CCME, 2001a). However, it is recognized that other PCB congeners (i.e., non-coplanar PCBs) may be missed with this approach. If dioxins and furans are also a contaminant of interest on site in addition to PCBs, consideration of PCBs along with dioxins and furans is recommended (as per CCME, 2001a), as these chemical groups share a common mode of action.

Evaluation of candidate TRVs

Table A.55. Candidate avian toxicity reference values (TRVs) for polychlorinated biphenyls (PCBs)

Candidate TRV (ng TEQ/kg bm/day)	Source (See Reference Section 3)
2.3	**CCME, 2001a**

There are other TRVs for specific PCB mixtures that have been presented in various sources. For example, CEAEQ (2012) presents avian TRVs based on toxicity of Aroclor 1254; Sample *et al.* (1996) presents avian TRVs for Aroclors 1242 and 1254. However, these, and other TRVs were not considered as candidate TRVs or included in Table A.55 above because of uncertainties and complexities of comparing toxicological data between data for PCB mixtures of different compositions. Individual PCB congeners vary by up to many orders of magnitude in their toxicity (CCME, 2001a). Therefore, different mixtures composed of varying congeners will also vary in their toxicity. Acute avian toxicity to PCBs generally increases with increasing chlorination, which is opposite to the relationship observed in mammals (CCME, 2001a). Estimated doses for PCB toxicity as reported in Appendix XIII of Environment Canada (2001) ranged from 0.34 mg/kg bm/day to 958 mg/kg bm/day for a variety of PCB formulations, species (e.g., chickens, ducks, owls, kestrels), endpoints (e.g., reproduction, survival), and effect levels (ranging from NOAELs to high effect levels like LC_{50}s). The selected TRV from CCME (2001a) was the only available TRV that evaluated toxicity data for a range of different PCB mixtures with varying compositions, by applying a toxic equivalency approach (Van den Berg *et al.*, 1998).

Suggestions for improved future TRVs

There are a wide range of avian PCB toxicity data available, but there were no available avian TRVs for PCBs that readily integrated toxicity data across multiple studies. Therefore, future effects assessments for PCBs could benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) to existing PCB toxicological data. Given the complexities of mixtures, careful TRV selection on a site-specific basis is likely required for PCBs. Considering the complexities and uncertainties unique to assessing complex PCB mixtures, effects characterization (and overall risk assessment) may be enhanced by considering a range of toxicity studies that are relevant to site-specific receptors and PCB mixture compositions present on site. For example, graphical exploration of available dose-response data and quantification of magnitude of effect size across multiple toxicological studies, species, endpoints, and mixture compositions (e.g., methods as illustrated in Hill *et al.*, 2014) will likely improve the overall effects characterization and assessment within an ERA, especially compared to relying on a single TRV. This type of approach for assessing effects (e.g., as described by Hill *et al.*, 2014) is an alternative to a single-TRV-based approach and is considered consistent with existing FCSAP TRV guidance (FCSAP, 2012b) and ERA guidance (FCSAP, 2010). Other types of information, such as effects measures based on diet concentration or tissue concentration, may also be investigated to further supplement and improve ecological risk assessments of PCBs within a weight-of-evidence approach.

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) [Dioxins and Furans]

Receptor: Birds

Selected TRV =4.47 ng TEQ/kg bm/day
Source: CCME, 2001b
Grade: C

Basis for the selected TRV

This TRV is also the basis for the current Canadian Tissue Residue Guideline for the Protection of Wildlife Consumers of Aquatic Biota (CCME, 2001a) (see CCME, 2001a for complete details on the derivation of this value selected as a default for FCSAP). It should be noted that the TRV for dioxins and furans is expressed in **units of ng toxic equivalency units (TEQs)/kg bm/day**. This TRV is based on the geometric mean of a NOAEL (0.014 µg/kg bm/day) and LOAEL (0.14 µg/kg bm/day) for egg production and embryo mortality in ring-necked pheasants dosed weekly via injection for 7 weeks (Nosek *et al.*, 1992). The study (Nosek *et al.*, 1992) was selected as the basis for the CCME (2001b) tissue residue guideline because it was the more sensitive study from a set of relevant studies, including a TDI (42.4 ng TEQ/kg bm/day) for white leghorn chickens calculated in CCME 2001b, although CCME 2001a also noted that white leghorn chicks may be inherently 10 times more sensitive to PCDD/F exposure than other avian species.

Merits of the selected TRV

The toxicological study was selected in consideration of a broad set of toxicological studies that included a range of species (e.g., chicken, dove, ducks, quail, herons, and terns) and is therefore likely to be protective of a range of avian species on federal contaminated sites. This TRV is also based on a relevant reproductive endpoint (egg production and embryo survival). As a unique issue to PCDD/F TRVs, this value applied toxic equivalency factors (TEFs), as recommended by the World Health Organization (van den Berg *et al.*, 1998), so that toxicities of PCDD/F mixtures with different congener compositions could be directly compared (see CCME 2001b for a description of TEFs and how they were applied in deriving this TRV).

Limitations of the recommended default TRV

The magnitude of effect associated with this TRV is not quantified because the TRV was derived as the geometric mean of a NOAEL and LOAEL value. Furthermore, the effect levels associated with the NOAEL and LOAEL underlying this TRV are not reported in CCME (2001b). Therefore, there is uncertainty behind the magnitude of effect associated with this TRV. An uncertainty factor of 10 was applied to adjust from a subchronic to chronic exposure duration in the underlying toxicological study and to account for interspecies sensitivity differences and exposure routes. The practice of applying uncertainty factors to correct for issues with experimental design is generally not recommended by FCSAP. Given the complexity of trying to characterize the effects of complex mixtures, this TRV is focused on the toxicity of 2,3,7,8-substituted PCDD/F congeners, which share a similar mode of action and are thought to elicit most or all of the toxicity of dioxins and furans (CCME, 2001b). However, it is recognized that other dioxin and furan congeners may be missed with this approach, and their toxicity is not well studied. If both PCBs and dioxins and furans are contaminants of interest on site, these groups of chemicals should be evaluated together given the shared mode of action between the coplanar PCB congeners and the 2,3,7,8-substituded PCDD/Fs.

Evaluation of candidate TRVs

Table A.56. Candidate avian toxicity reference values (TRVs) for dioxins and furans

Candidate TRV (ng TEQ/kg bm/day)	Source (See Reference Section 3)
4.47	**CCME, 2001b**

The selected TRV has various merits and limitations (described above). CCME (2001b) presented this TRV following a comprehensive review of available toxicological data and may therefore be used as a default value for FCSAP. CCME (2001b) also summarized a broader set of available toxicological data for PCDD/Fs. Because of the uncertainties inherent in assessing toxicity of a mixture of chemicals like PCDD/Fs (on top of other generic limitations of TRVs), consideration to as broad a set of toxicity data as possible (e.g., as summarized in CCME, 2001b) should be given on a site-specific basis when selecting a TRV or method for effects assessment that is best suited for specific receptors of concern, especially where risk at a site is being driven by this contaminant.

Suggestions for improved future TRVs

Available avian PCB toxicity data are somewhat limited and most are focused on 2,3,7,8-TCDD (CCME, 2001b). Future effects assessments for dioxins and furans could benefit from application of FCSAP's recommended TRV derivation methodology (FCSAP, 2010b) to existing PCDD/F toxicological data. Given the additional complexities of mixtures, careful TRV selection on a site-specific basis is likely required for PCDD/Fs. Considering the complexities and uncertainties unique to assessing complex PCDD/F mixtures, effects characterization (and overall risk assessment) may be enhanced by considering a range of toxicity studies that are relevant to site-specific receptors and dioxin and furan congeners present on site. For example, graphical exploration of available dose-response data and quantification of magnitude of effect size across multiple toxicological studies, species, endpoints, and mixture compositions (e.g., methods as illustrated in Hill *et al.*, 2014) will likely improve the overall effects characterization and assessment within an ERA, especially compared to relying on a single TRV. This type of approach for assessing effects (e.g., as described by Hill *et al.*, 2014) is an alternative to a single-TRV-based approach and is considered consistent with existing FCSAP TRV guidance (FCSAP, 2012b) and ERA guidance (FCSAP, 2010). Other types of information, such as effects measures based on diet concentration or tissue concentration, may also be investigated to further supplement and improve ecological risk assessments of dioxins and furans within a weight-of-evidence approach.

APPENDIX B: METHODS FOR TOXICITY REFERENCE VALUE EVALUATION AND SELECTION

B.1. Toxicity Reference Value Sources and Compilation

To select the recommended default TRV for use on FCSAP sites, candidate TRVs were sourced from previous FCSAP work related to TRVs and from references provided in Table 1 of the *FCSAP Ecological Risk Assessment Guidance Module 2: Selection or Development of Site-specific Toxicity Reference Values*; (FCSAP, 2010b). A summary of the general methods and characteristics associated with TRVs derived or reported in each of these sources is presented in **Appendix C**. Additional TRVs were also requested from federal FCSAP and contaminated sites working groups, as well as other ERA practitioners with an interest in FCSAP and/or ERAs. Primary literature and other publicly available reports (e.g., Superfund risk assessments) were also reviewed to identify any additional candidate TRVs to be considered as defaults for FCSAP.

From these sources, all available candidate TRVs were compiled for two receptor groups (i.e., mammals and birds) and five contaminant groups: 15 metals; 7 polycyclic aromatic hydrocarbons (PAHs); volatile organics (benzene, toluene, ethylbenzene, and xylenes, collectively referred to as BTEX); petroleum hydrocarbon (PHC) fractions (F1, F2, F3, F4, and total PHCs); and polychlorinated biphenyls (PCBs).

B.2. Toxicity Reference Values Evaluation Methodology

Candidate TRVs for each receptor and contaminant (e.g., lead TRVs for mammals) were evaluated against a set of 10 specific criteria to determine how well aligned each TRV is with respect to the level of protection expected for a default value used on FCSAP sites and with respect to published FCSAP guidance on TRV derivation methodology (FCSAP, 2010b). These criteria and their methods of evaluation are described in detail in Table B1. The 10 evaluation criteria used were assembled into a Microsoft Excel-based matrix, and every candidate TRV was evaluated against each criterion to assess its merits and limitations. (Excel-based matrices for individual contaminants and receptors are available upon request from Environment and Climate Change Canada). The candidate TRV with the most merits and fewest limitations was selected as the recommended default FCSAP TRV. When multiple TRVs were found to be equal in merit, the lower number was selected as a conservative approach for FCSAP until future investigations may resolve any unknowns or discrepancies between similarly ranked TRVs.

FCSAP recognizes that TRVs conforming to all 10 evaluation criteria evaluated may not exist; however, each of the TRVs evaluated may have their own individual merits and limitations. It is also recognized that some of the candidate TRVs evaluated for the purposes of selecting a default value for FCSAP may have been derived using methods that do not follow the recommendations laid out in the published FCSAP guidance on TRV derivation methodology *(*FCSAP, 2010b). For example, the guidance generally

advises against the use of allometric scaling and the application of generic uncertainty factors. In addition, TRVs derived from NOAELs or LOAELs are limited in part because they do not quantify the level of effect with which they are associated. While these methods are generally discouraged when developing new TRVs, FCSAP recognizes that significant data limitations may exist and that readily available and/or published TRVs may have used some of these methods. Regardless, the resulting TRVs may be the best available option for a default value at this time.

This project evaluated only established, readily available TRVs and did not derive any new TRVs from raw toxicity data. This evaluation relied upon the data quality assessment and screening applied by the original TRV's source. Individual data quality screening and evaluation is a significant task beyond the scope of this project; therefore, if the source of a TRV (e.g., USEPA) considered the toxicity data suitable to be included in their dataset, then the overall assessment by that source was further relied upon in evaluating the TRV.

Each contaminant/receptor pair was assigned one of the following five grades based on overall consistency with FCSAP guidance for TRV derivation and degree of confidence in overall suitability as a default for federal contaminated sites:

Grade A: Recommended as a default TRV for FCSAP, generally consistent with FCSAP TRV guidance, and high degree of confidence in its overall suitability as a default for federal contaminated sites.

Grade B: Recommended as a default TRV for FCSAP, but with some inconsistencies with FCSAP TRV guidance, and moderate degree of confidence in its overall suitability as a default for federal contaminated sites.

Grade C: Recommended as a default TRV for FCSAP, but with substantial inconsistencies with FCSAP TRV guidance and low degree of confidence in its overall suitability as a default for federal contaminated sites.

N/S None Suitable. No TRV was recommended as a default for FCSAP because none of the available TRVs were considered suitable to meet FCSAP criteria.

N/A None Available. No TRV was recommended for FCSAP because none were available for evaluation.

Selected TRVs in all three categories are accepted for use on FCSAP sites. TRVs that were evaluated but not selected (see **Appendix A** for not-selected TRVs) will not be accepted for use as a default on FCSAP sites. Selection of a TRV assigned any of the above grades does not preclude consideration of other TRVs not yet evaluated, particularly if they address the limitations outlined for individual contaminants and receptors in **Appendix A**. Furthermore, selection of a TRV does not preclude development of site-specific TRVs following FCSAP guidance (FCSAP, 2010b).

Table B.1.: Criteria and method of evaluation used to evaluate TRVs against FCSAP guidance and program objectives.

Evaluation Criteria		*Method of Evaluation*
1.	Is the TRV based on multiple toxicity studies from reliable sources? Select from: *<5 studies,* *≥ 5 studies, or* *Do Not Know.*	The derivation of a TRV should be based on the best available data; however, the reality is that there are generally very limited reliable and robust toxicity data for wildlife species in the published literature. Additionally, new wildlife studies are typically published at a very slow rate. In such cases, a TRV can be derived from a single literature study or very small number of studies that determine the dose/concentration and effect size without quantifying the underlying relationship. TRVs based on multiple toxicity studies from reliable sources are ideal, yet not always available. This question should be evaluated in consideration of all the studies investigated to derive the TRV. For example, if 15 studies were considered and the final TRV selected was a no observed adverse effect level (NOAEL) from one particular study, the proper response to select would be "≥ 5 studies". If it is unclear how many studies were considered for the TRV derivation, please select "Do Not Know".
2.	Is the TRV based on dose-response or LOAEL/NOAEL methods? *Select from:* *Dose-response or* *LOAEL/NOAEL.*	The preferred derivation method for TRVs uses dose- or exposure-response data from studies that tested multiple doses or exposure concentrations and quantifies the effect size, or dose- or concentration-response relationship. However, for many substances, adequately robust toxicity data do not exist to enable the development of such TRVs. As a result, TRVs based on NOAELs and LOAELs from toxicological studies are widely available and commonly used when dose-response methods are not feasible or available. Key criticisms of NOAEL- and LOAEL-based TRVs include the following: they are not innately related to biologically relevant thresholds; they do not provide information about the actual magnitude of effects in the reported studies; they do not necessarily equate to a ''no effect'' dose (i.e., they reflect only the test concentrations used in the study and are strongly influenced by factors related to statistical power, such as study design, numbers of test animals and replication); studies with fewer test animals are more likely to over-estimated a true "no effect" dose (Brown and Erdreich, 1989); NOAELs and LOAELs can be based on judgment; and, they potentially ignore information describing the complete dose-response relationship and instead focus on a single point on the dose-response curve.

Evaluation Criteria		Method of Evaluation
3.	If based on LOAEL/NOAEL, are they bound or unbound? *Select from:* *Bound,* *Unbound,* *Mixed,* *Not Applicable, or* *Do Not Know*	Bound values come from studies with both a NOAEL and LOAEL reported, and there is usually some certainty as to the test doses/concentrations at which effects begin to occur and at which effects do not occur. Unbound values are often single NOAEL or LOAEL values from studies that lack information on the dose- or exposure-response at lower or higher test concentrations/doses. It is generally considered that bound toxicity data is preferred as there is greater certainty as to the dose or concentration range where effects begin to occur. The response to this question is subject to reviewer judgment and interpretation. As guidance, a TRV that uses a mixture (approximately 50%) of bound and unbound values can be considered "Mixed". If the mixture is predominantly (e.g., >75%) bounded or unbounded, please select the response that reflects this majority ("Bound" or "Unbound"). If the TRV is based on dose-response data, please select "Not Applicable". If unclear from the information provided, please select "Do Not Know".
4.	Was allometric scaling used for interspecies extrapolations? *Select from:* *Yes,* *No, or* *Do Not Know*	Allometric scaling is a toxicological extrapolation method in which simple mathematical calculations are used to scale the dose rates of contaminants from one species to another in relation to proportional changes in body size. Allometric scaling is based on the principle that species sensitivity is a function of basal metabolic rate, which is related to body mass. For example, laboratory-based mouse toxicity data for arsenic may be converted with allometric scaling to estimate an arsenic TRV for a species like deer with a larger body mass. Allometric scaling is not always appropriate for various reasons: factors other than basal metabolic rate may influence species sensitivities (e.g., gastrointestinal physiology); evidence of scaling factor effectiveness is often based on acute toxicity data; and evidence suggests that allometric scaling is not applicable to bird species.
5.	Were uncertainty factors applied? *Select from:* *Yes,* *No,* *Yes but with scientifically sound*	Uncertainty factors are often applied to TRVs to address underlying uncertainties, such as extrapolating data from the laboratory to the field, from acute to chronic, or between taxa. Uncertainty factors add an extra margin of safety to empirical data. However, they are typically somewhat arbitrary rather than being based on quantitative, scientific rationale. The use of uncertainty factors is generally discouraged, but often times their application may be more appropriate than not applying an uncertainty factor at all. For example, a TRV based on acute data plus an uncertainty factor is likely more useful than a TRV based only on acute data (no uncertainty factor). Please use discretion when answering this question.

Evaluation Criteria		Method of Evaluation
	rationale, or *Do Not Know*	
6.	Has the TRV been derived from data that is adequate for the receptor of concern it intends to protect? *Select from:* *Yes,* *No, or* *Do Not Know*	The data used to develop a TRV should be appropriate for the species for which the TRV is derived. For example, if a TRV has been developed for all mammals, have several different species been considered (>5) in the derivation process? Consideration of only one or a few species for the selection of a mammal TRV does not account for variations in species sensitivities and is not considered good practice. It is important to note that this question should be answered in regard to the methodology used to select the TRV and not just the final TRV itself. For example, if bound LOAEL/NOAEL data from 50 toxicological studies were considered and the final mammal TRV was selected as the highest bounded NOAEL below the lowest bound LOAEL (data from one single rat study), this would be considered to have been derived from data that is adequate for the receptor of concern it intends to protect (i.e., more than five species). The derivation method has demonstrated that the mammal TRV is at a dose-level that does not result in effects in all other mammal species. Therefore, while the final mammal TRV selected is from one study, it can be considered to be protective of all mammals because of the manner in which it was derived.
7.	Does the TRV use acceptable biological endpoints? *Select from:* *Yes,* *No, or* *Do Not Know*	Survival, growth and reproduction are considered to be appropriate biological endpoints for FCSAP, as they can be easily and intuitively extrapolated to estimate potential effects on populations or communities. In other words, these endpoints have a sufficiently severe consequence that the implications of impaired growth, reproduction or increased mortality could potentially be observed in affected populations or communities. Conversely, the biological significance of less severe endpoints (e.g., enzyme changes in individual organisms, immunosuppression) is much more difficult to extrapolate to higher levels of biological organization, as the consequence of such effects at a larger biological scale is more uncertain. TRVs derived from endpoints other than growth, reproduction or mortality may be suitable if impacts are demonstrated to be relevant to higher levels of biological organization. If endpoints used are not considered to have an impact beyond individual level, please select "No". If it is unclear from the information provided which biological endpoints were used, or relevance beyond the individual level for the described endpoint is uncertain, please select "Do Not Know".

Evaluation Criteria		Method of Evaluation
8.	Are the data and toxicity tests underlying the TRV reflective of actual conditions? *Select from:* *Yes,* *No, or* *Do Not Know*	Underlying toxicity testing and derivation methods need to be consistent with the ecological processes actually occurring in the field. For example, bird and mammal TRVs should be based on exposures through oral ingestion toxicity studies, preferably through diet, as these generally represent the actual routes of exposure that are likely to be occurring on federal contaminated sites. Studies using gavage methods are considered to have limited representation of ecologically relevant exposure conditions (e.g., through diet). Exposure pathways other than directly via diet or injection (such as maternal transfer) may also be relevant for certain contaminants (e.g., lead, PCBs) and may be more specifically addressed in the development of future or site-specific TRVs, but were not directly considered here. Other factors that may be considered when answering this question include duration of underlying toxicity test(s) (e.g., a 2-year study may be more relevant than a two-day study) and whether the toxicological data were collected in a laboratory- or field-setting. When a TRV was based on multiple studies (as is typically the case with USEPA TRVs), this criterion was applied to the entire dataset as a whole, not just the single study from which the numerical TRV came from.
9.	Does the TRV provide a level of protection that is consistent with minimal to low level of effects or is it overly conservative? *Select from:* *Yes,* *No,* *Overly Conservative, or* *Do Not Know*	Default FCSAP wildlife TRVs are selected with the intention of providing a conservative level of protection that is consistent with the level of protection inherent in the Canadian Council of Ministers of the Environment (CCME) soil quality guidelines (CCME, 2006). For the purposes of selecting default values in this module, the intended narrative protection goal was considered to be met when there are no more than minimal to low effects to common species, as long as there are no long-term adverse effects on the local populations or ecosystem functions. Again, for the purposes of selecting default values in this module, TRVs that could be demonstrated to be based on an effect level of 25% or less (i.e., EC_{25}/IC_{25}; CCME, 2006, Section 7.5.5) were considered to represent minimal to low effects to common species. This question evaluates the level of effect associated with TRVs. This project focused on generic mammalian or avian TRVs. Therefore, for this evaluation, an effect level of less than or equal to 25% (e.g., 25% reduction in reproduction endpoint) was considered appropriate for FCSAP sites. TRVs based on an effect level closely matched to 25% (e.g., EC_{20}) were considered to provide an acceptable level of protection as a default TRV. Quantified effect levels were preferred over NOAELs and LOAELs. NOAELs and LOAELs are often associated with uncertain effect levels (see Question 2 in this table) and may be

Evaluation Criteria	Method of Evaluation
	overly, sufficiently, or under-protective for FCSAP, depending on their derivation methodology and other available toxicity information. For example, a TRV-based on a NOAEL may be considered overly protective if it was developed in consideration of a large number of studies and if there were few or no LOAELs observed below the TRV. However, a TRV based on a NOAEL from only a single study may be considered to have an unknown level of protection, particularly if other available TRVs had a similar value but were based on a LOAEL or EC_{25}. TRVs derived from LOAELs should be further investigated in order to try to quantify their associated effect levels. LOAELs have the potential to be associated with greater than 25% effect level, which would be under-protective as a default value for FCSAP. Risk assessments at FCSAP sites may require selection and development of site-specific TRVs that meet species-specific protection goals mandated by the *Species at Risk Act*, the *Migratory Birds Convention Act*, *1994*, and the *Fisheries Act*. Other protection goals not explicitly considered in the selection of default wildlife TRVs for FCSAP include no effect on individuals of protected species (to comply with the *Species at Risk Act*), no deleterious effects to fish (to comply with the *Fisheries Act*), no effects to migratory birds (to comply with the *Species at Risk Act* and *Migratory Birds* Convention Act, 1994) and only minimal to low effects to common species provided there are no long-term, adverse effects on the local populations or ecosystem functions. For example, a 10% reduction in a reproductive endpoint may be considered a minimal to low effect size for mice and is unlikely to have substantial population-level effects. However, the same effect level, i.e., 10% reduced reproduction, could have a significant adverse effect on grizzly bear populations. Furthermore, FCSAP protection goals require that there are no other socio-economic reasons for which minimal effects would not be considered acceptable (e.g., culturally-important species). These additional protection goals should also be addressed, particularly on a site-specific basis, but are beyond the scope of selecting default wildlife TRVs for FCSAP. FCSAP recognizes that TRVs derived from toxicity data that exactly match these protection goals are not always possible (e.g., toxicity data for a bear). A range of TRVs may be considered to meet these FCSAP protection goals, while some TRVs may be conservative and provide a higher level of protection beyond FCSAP's minimum level of protection. This evaluation aims to select the TRV that best aligns with published FCSAP guidance (FCSAP, 2010b), considering the merits and limitations of currently available TRVs.

Evaluation Criteria	*Method of Evaluation*
10. Do any major concerns exist that would preclude the use of this TRV by FCSAP? *Select from:* *Yes,* *Minor Concerns, or* *No*	Questions 1 through 9 evaluate key aspects of TRV derivation and applicability for use in the FCSAP program. However, other potential issues with TRVs may exist that are not captured in these questions, such as a lack of information required to answer all evaluation questions, or inconsistencies between various TRVs being evaluated. This question should also consider the culmination of limitations across all evaluation criteria. For example, a TRV derived from a single study for a single species and single endpoint and to which uncertainty factors and allometric scaling is applied has many limitations, which leads to reduced confidence that the TRV is representative of a broad range of ecologically relevant exposure conditions. TRVs with these types of potential issues may not be reliable or appropriate for use on federal contaminated sites. If concerns exist that would preclude the use of the TRV as a default recommended TRV for FCSAP, please select "Yes" and describe your concern in the Notes section. Minor concerns are those that could be resolved with further investigation and should be addressed before recommending the TRV as a default FCSAP TRV. Please use your professional judgment when responding to this question.

APPENDIX C: SOURCES FOR CANDIDATE TOXICITY REFERENCE VALUES

Table C.1.: Overview of the sources for published primary toxicity reference value (TRVs) that were consulted to identify candidate default TRVs for evaluation as potential FCSAP recommended default TRVs (adapted from Table 1 in FCSAP, 2010b). In addition to the sources listed in this table, additional TRVs were also solicited from ERA practitioners and searched for in primary literature and other publicly available reports.

TRV source[1]	Underlying toxicological data	TRV derivation methods	Uncertainty factors/ allometric scaling	Species covered	Endpoints	Effect levels	Merits	Limitations
USEPA, 2005a; 2005b; 2005c; 2005d; 2005e; 2007a; 2007b; 2007c; 2007d; 2007e; 2008	Uses multiple studies to create a database of NOAELs and LOAELs	TRV is either a geometric mean of NOAELs (if lower than lowest bound LOAEL) or the highest bound NOAEL lower than the lowest bound LOAEL	None	Birds and mammals Number of species depends on the size of the database	Reproduction Growth Survival[2]	NOAELs	Comprehensive literature review Possibility of a TRV based on multiple species	TRVs based on a NOAELs (either a single NOAEL or a geometric mean of several NOAELs)
Sample *et al.*, 1996	A literature search using databases and reference lists was conducted to identify candidate studies for TRV development	TRVs reported as NOAELs and LOAELs calculated from a single selected study	Uncertainty factors for converting chronic to subchronic and LOAELs or LD50s to NOAELs	Birds and mammals Most TRVs are based on one or a few species	Reproduction Growth Survival	NOAELs and/or LOAELs	Summary of studies provided Important information (including dose-levels) provided in summary	TRV based on NOAEL or LOAEL Only a single study is reported, even if many were considered

TRV source[1]	Underlying toxicological data	TRV derivation methods	Uncertainty factors/ allometric scaling	Species covered	Endpoints	Effect levels	Merits	Limitations
CEAEQ, 2012	The literature was searched to choose suitable studies on the basis of CEAEQ data quality criteria	Weibull model is fitted to dose-response data from each study data, and EC_{10}, EC_{20}, or EC_{40} were calculated from each estimated dose-response curve The lowest EC_{10}, EC_{20}, and EC_{40} across all studies is selected as the TRVs	Allometric scaling (mammals) Uncertainty factors for short test durations and survival endpoints	Birds and mammals Usually, few species are investigated	Reproduction Growth Survival	EC_{10}, EC_{20}, EC_{40}	Dose-response curves provide an EC_{20} or EC_{40} Includes more than one study Confidence in underlying toxicological data was scored based on its assessed quality and relevance Easy to access values (presented in units of mg/kg bm/day)	Allometric scaling used for mammals Uncertainty factors used to convert acute studies to chronic studies
CEAEQ, 2000	Primarily based on data in Sample *et al.* (1996)	NOAELs and LOAELs were adjusted to approximate EC_{10}, EC_{20}, and EC_{40} Detailed information on this methodology was not available	Uncertainty factors for short test durations, and survival endpoints.	Birds and mammals	Reproduction Growth Survival	Approximated EC_{10}, EC_{20}, and EC_{40}	Attempted quantification of effect level	Allometric scaling used for mammals Uncertainty factors used to convert acute studies to chronic studies
OMOE, 2009, 2011	Most TRVs are taken from CCME soil quality guidelines or Sample *et al.* (1996)	TRVs reported as LOAELs	Uncertainty factors may be used, but not systematically	Birds and mammals Usually, one species per TRV	Reproduction Growth Survival	LOAEL	Easy to access values (presented in units of mg/kg bm/day)	Geared towards Ontario VECs LOAEL methodology Underlying studies may be hard to find

TRV source[1]	Underlying toxicological data	TRV derivation methods	Uncertainty factors/ allometric scaling	Species covered	Endpoints	Effect levels	Merits	Limitations
USEPA Region 9 BTAG, 2009	Not available	TRVs reported as low TRV (NOAELs) and high TRV (LOAELs) calculated from a single selected study	Not available	Birds and mammals One species per study	Reproduction Growth Survival Other (e.g., cancer, tumours, immunotoxicity, behavioural)	NOAELs and LOAELs	Easily accessible values for the listed contaminants (presented in units of mg/kg bm/day)	Information on the TRV derivation methodology is mostly unavailable Likely derived from single selected study
LANL, 2014	A literature search is conducted and TRVs are established for each contaminant	Either a geometric mean of the NOAEL or a value based on a critical study (NOAEL or LOAEL)	Uncertainty factors often used to convert acute data to chronic or to convert LOAELS/NOAELs to NOAELS/LOAELs	Birds and mammals Only one species if critical study	Reproduction Growth Survival	NOAELs and LOAELs	Values available for many contaminants Clear methodology and detailed descriptions of underlying toxicity data Considers multiple studies, where possible	Uses uncertainty factor Based on NOAELs/LOAELs; effect size not quantified Unknown reasons for the choice of a given study
USEPA, 1999	Selected TRV from i) Sample *et al.* (1996), and ii) USEPA EcoTox database.	Once toxicity data were compiled, reviewed, and screened out if experimental design deemed inappropriate, typically the lowest value was selected as the TRV	Uncertainty factors applied in some cases, to extrapolate a reported toxicity value to a chronic NOAEL TRV	Birds and mammals	Varied, but includes reproduction, growth, and survival	The lowest available value was selected, which was typically a NOAEL (either empirical, or calculated)	Relevant endpoints for FCSAP protection goals	Use of uncertainty factors not strongly supported by scientific rationale lead to potentially overly conservative TRVs
Allaway and Stodola, 2011	Primarily consulted Sample *et al.* (1996) and OMOE (2009) Also considered other TRV sources where data were limited	Did not derive new TRVs, but rather evaluated existing TRVs available from published sources	Uncertainty factors applied in some cases TRVs that used allometric scaling were generally not selected	Birds and mammals	Reproduction Growth Survival	LOAELs preferred; NOAELs only if LOAEL or $EC_{20/25}$ not available	Considered a broad variety of TRV sources	Effect level associated with selected TRVs is not quantified Selected TRVs are primarily based on a single study

TRV source[1]	Underlying toxicological data	TRV derivation methods	Uncertainty factors/ allometric scaling	Species covered	Endpoints	Effect levels	Merits	Limitations
Dillon Consulting Ltd., 2013	Consulted eight different TRV sources (including Sample *et al.*, 1996)	Did not derive new TRVs, but rather evaluated existing TRVs available from published sources	In some cases, uncertainty factors were reduced or removed TRVs that used allometric scaling were not accepted	Birds and mammals	Reproduction Growth Survival	LOAELs considered most likely to provide a level of protection that is consistent with minimal to low level of effects NOAELs also considered in context of other available toxicity information	Considered a broad variety of TRV sources Acknowledgement of general limitations of presently available TRVs (e.g., single study)	Effect level associated with recommended TRVs is not quantified Several selected TRVs are primarily based on a single study Does not include a complete detailed summary of all TRVs that were evaluated

$EC_{10}/_{20}/_{40}$ = effect concentration corresponding to a 10%/20%/40% effect level; FCSAP = Federal Contaminated Sites Action Plan; LOAEL = low observed adverse effect level; NOAEL = no observed adverse effect level; TRV = toxicity reference value; VEC = valued ecological component.

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2. Other endpoints (e.g., behaviour) also included in USEPA data compilations, but were not directly included in TRV derivation.

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Additional information can be obtained at:

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