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STANDARD PRACTICE FOR WILDLIFE TOXICITY REFERENCE VALUES

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U.S. ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE

Environmental Health Risk Assessment Program

Health Effects Research Program

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- Environmental Health Risk Assessment Program
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This technical guide and a current listing of wildlife toxicity assessments are available at the following website:

http://chppm-www.apgea.army.mil/tox/herp/wta.htm

FORWARD

This technical guide provides our Center's standard practice for the development and documentation of wildlife toxicity reference values, which are used to assist in the evaluation of risks that military-related chemicals may pose for environmental quality. Informed and defensible environmental health risk management is limited by the quality of the risk assessments used to support them. Therefore, this technical guide is designed to improve the analyses behind these risk management decisions. It is written primarily for risk assessors.

This technical guide should not be construed as official Department of the Army policy unless so designated by other authorizing documents. This document provides guidance and technical reference material based on scientific information current at the time of publication. As available information and supporting data are continuously being advanced, users are cautioned to ascertain existence of any updated information.

The Surgeon General is responsible for providing policy and technical expertise on human health and ecological aspects of pollution resulting from Army activities and operations (Army Regulation 200-1 (AR 200-1) Environmental Protection and Enhancement and AR 40-5 Preventive Medicine). The Surgeon General has delegated this responsibility through the U.S. Army Medical Command to the U.S. Army Center for Health Promotion and Preventive Medicine. This guide was developed pursuant to this authority.

TABLE OF CONTENTS

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USACHPPM TECHNICAL GUIDE NO. 254

STANDARD PRACTICE FOR WILDLIFE TOXICITY REFERENCE VALUES

1. Introduction

1.1 Purpose

This U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254 (USACHPPM TG 254) outlines a Standard Practice that establishes a methodology for—

- Generating defensible wildlife **toxicity reference values** (TRVs)[1] for chemicals of interest in Army ecological risk assessment (ERA) programs.
- Preparing the documentation to support such TRVs. A wildlife TRV is similar to a human health **reference dose** (RfD)[2].

1.2 Audience

Ecological risk assessors and toxicologists are the target audience for this Standard Practice. Army risk managers and staff responsible for coordination of ERA programs should ensure that their project teams consider this Standard Practice during project design and implementation.

1.3 Application

This TG is primarily intended for use by this Center to generate wildlife TRVs for military-related substances that are more defensible than those typically used in many U.S. Army risk assessments. If a TRV relevant to a particular ERA has been generated by this Center using this methodology, then its use is expected unless an alternative can be reasonably defended. This Center will apply the methodology in a phased approach, focusing upon the highest priority chemicals first. Other U.S. Army and military entities are encouraged to use this Standard Practice within their ERA programs.

1.4 Limitations of Use/Exceptions

By definition, the procedures described herein result in measures of toxicity (i.e., TRVs) that evaluate the likelihood of effects in *individual* organisms that may be relevant to a *population* of organisms in the wild. This TG does not specifically address how the measures, or resulting risk estimates, relate to **demographic rates** (or outcomes) for any particular population of interest. These methods create a biased risk estimate for use in screening-level evaluations. Assessing risk to populations involves using these methods and other lines of evidence[3] before any risk management action to protect populations can be recommended based upon scientific information.

Methodological exceptions to this Standard Practice may be warranted in some circumstances. These circumstances are—

- When the procedures are not consistent with promulgated Federal or state law.
- When the ERA documents persuasive scientific evidence, or argument, to bear on the specific issue in question.

1.5 TG Revisions

This TG will be reviewed on a regular basis. If the Standard Practice is determined to be inconsistent with current procedures and/or regulations, it will be revised and reissued with an appropriate revision number.

This TG may also be revised, as appropriate, when the ongoing U.S. Environmental Protection Agency (USEPA) collaborative effort to develop guidance for ecological soil screening levels (EcoSSLs) is finalized.

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[1] Definitions of terms in bold-faced font are provided in Appendix B.

[2] This document uses the term 'wildlife' to specifically refer to *vertebrate* organisms other than fish that live in the wild.

[3] For example: site-specific fieldwork, evaluations of reproductive success, demographic (population) modeling, and/or biological monitoring.

1.6 Background

An integral component of a wildlife ERA is the development of some quantitative measure of the toxicity of a chemical to the animals (or receptors) of concern. Toxicity measures that are employed in Army programs have not been consistent or, in some cases, necessarily defensible.

2. Methodology

In general, TRVs are needed to represent levels of exposure that are associated with low risk for entire **taxonomic** classes (e.g., mammals) or for selected foraging **guilds** (e.g., carnivorous mammals). This TG focuses upon the development of chemical-specific TRVs for these receptor groups.

The methodology for generating defensible wildlife TRVs and for preparing acceptable documentation to support such TRVs consists of two phases.

a. **Phase 1 – Toxicity Profile**
   (1) Perform data collection and literature search.
   (2) Identify relevant studies.
   (3) Prepare a toxicity profile.

b. **Phase 2 – TRV Report**
   (1) Derive TRVs and document selection rationale.
   (2) Assign confidence levels to the TRVs.
   (3) Prepare the TRV report.

The outcome of these two phases are combined into a comprehensive "wildlife toxicity assessment" for the chemical(s) under review. Each wildlife toxicity assessment report shall contain a list of the primary author(s), contact information, and a report date.

2.1 Data Collection/Literature Search

The literature search will provide—

- Qualitative information on the toxicological characteristics of the chemical(s) under consideration.
- A set of relevant studies that may be used in the development of TRVs.

All appropriate sources should be searched for specific toxicological information for mammals, birds, and herpetofauna. Presently, there is no single source that provides a comprehensive review for substances of concern. Potential sources include:

- TOXLINE (National Library of Medicine),
- ATSDR Toxicity Profiles
- BIOIS (Biological Abstracts),
- Hazardous Substances Data Bank (National Library of Medicine),
- Integrated Risk Information System (IRIS),
- ECOTOX database (USEPA, Duluth),
- Medline (National Library of Medicine),
- Registry of Toxic Effects of Chemical Substances (RTECs), and
- Toxicological *Benchmarks for Wildlife* (Oak Ridge National Laboratory) [Sample et al. 1996].

A thorough examination of the toxicological literature is necessary to support and defend any toxicity measure used in risk assessments. Although up-to-date toxicity information is important, useful updates for ERAs are infrequent. To ensure that all potentially relevant information is collected, the literature search should be inclusive of all intra-class foraging guilds (e.g., small mammalian herbivores and mammalian invertivores).

Unpublished data that are scientifically defensible can be used if the data (or study) is provided in the final wildlife toxicity assessment report.

When toxicity data are unavailable for a class of animals (e.g., birds), data from other classes of animals will not be used to derive a quantitative measure of toxicity[4]. Physiological differences between taxonomic classes are assumed to be too great to make any **extrapolation** useful in predicting effects to another taxonomic class of animal (e.g., using mammal data for birds). This science-policy choice is based on three points.

a. As the taxonomic distance increases between any two groups of organisms, physiological differences increase and the uncertainty associated with toxicity extrapolations across those taxa increases [Suter 1993]. This has been recognized by the USEPA who state that

[4] An appropriate exception is when the mechanism of toxicity is clearly known and an understanding of the physiological differences allows for extrapolation.

"whatever methods are employed...it is important to apply the methods in a manner consistent with sound ecological principles and the availability of an appropriate database" [USEPA 1998, p. 26878].

b. Extrapolations between two species may be more credible if factors such as similarities in food preferences, body mass, physiology, and seasonal behavior are considered [Sample et al. 1996, USEPA 1998].

c. Extrapolation requires context, and employing the use of large (3 or 4 orders of magnitude) uncertainty factors is unrealistic as identified in current guidance [Chapman et al. 1998, USEPA 1998, USACE 1996].

In these cases, the following strategies can be used to assist in an ERA although they do not produce TRVs. Other strategies than those listed here may be appropriate; however, they should be based upon site-specific conditions.

a. Acknowledge the uncertainty due to the lack of appropriate data. Qualify the extent and direction in which inter-class physiological differences are expected to influence any toxicity estimate.

b. Apply methods using Quantitative Structure-Activity Relationships (QSARs) to estimate the toxicity when there is information on a structurally similar organic substance that has a suspected similar mode of action. This alternative is useful when assessments have historically used a chemical presumed to be the most toxic of a class of chemicals. For example, using the benzo(a)pyrene TRV for other similar polycyclic aromatic hydrocarbons (PAHs) when no useful toxicity data are available for other PAHs.

c. Employ alternative lines of evidence for assessing ecological risk. Examples are:

- Measures of the likelihood of exposure given availability and quality of habitat;
- Measures of spatiotemporal scale of the extent of contamination;
- Measures of species diversity/abundance, toxicity tests; and
- Measures of fitness, and reproductive performance.

Predominantly, the data collection/literature search effort will result in identifying relevant controlled toxicity studies. Tissue investigations and field evaluations rarely provide appropriate cause-and-effect data that are helpful in deriving TRVs. However, this information should be provided and discussed in the toxicity profile, if applicable.

2.2 Identification of Relevant Studies

After the data collection/literature search effort is completed, the studies that are relevant to the development of TRVs applicable to wildlife need to be identified.

The paragraphs below discuss the criteria used to select toxicity data relevant to TRV development. The available studies in the literature may not satisfy all of these criteria; therefore, those studies that satisfy as many of these criteria as possible will be considered relevant. In most cases, it is expected that a small set of studies will be identified that are 'nearly equivalent' in terms of their relevance.

a. The toxic effects identified are most clearly linked to factors suspected to greatly influence population sustainability (i.e., demographic rates: birth, death, and dispersal rates). Prior knowledge of factors most relevant in population-specific regulation is needed. More often than not, this information will not be available specific to the animals of concern. In this case, choosing the **endpoints** that are protective of the other endpoints is recommended (i.e., considering sensitive endpoints). Toxicological endpoints should be evaluated in terms of their relevance to the health and ecology of the whole organism(s). Several endpoints that satisfy these criteria are-

(1) Mortality.
(2) Reproduction.
(3) Development.
(4) Growth.
(5) Behavior relevant to reproduction, feeding, and predator avoidance.
(6) Decreased resistance to disease (stress).

Other indirect acting endpoints may also be important. Examples may include factors that influence energy allocation that may indirectly influence reproductive performance and success. In the absence of sound ecological knowledge for the species' of concern, these endpoints must be considered as nearly equivalent.

This criterion is designed to focus TRV development on the types of wildlife health effects that are most relevant to risk management goals. It assumes that the goal is to protect against a decline in a wildlife population. Therefore, the most important toxic endpoints are those listed above in the order of their theoretical relative importance to population sustainability. This criterion is consistent with USEPA guidance [USEPA 1997, pp. 1-9].

b. The exposure duration in each study should be clearly identified. Typically, chronic exposures should be most protective, thus most relevant. However, given the differences in species response, methods, observed effects, dispersal characteristics and habitat use in the field, and all potential toxicological endpoints, all exposure periods should be considered. The following guidelines are used to determine the exposure duration of a toxicity study:

    (1) Chronic exposures are considered to be those equal to or greater than 10% of the life span of the test organism. An exception to this criterion is when exposure occurs during a sensitive life stage such as gestation. Classifying such tests as "chronic" is considered reasonable for endpoints specific to that life stage (e.g., embryo development and clutch size).

    (2) Subchronic exposures are considered to be those repetitive exposures less than 10% of the life span of the test organism, yet greater than 14 days.

    (3) Acute exposures are considered to be those of a single or repetitive exposure less than 14 days or 10% of the life span of the test organism.

These exposure duration definitions were developed primarily from USEPA regulations concerning regulatory toxicity testing under the Toxic Substances Control Act (TSCA) and the Risk Assessment Guidance for Superfund [USEPA 1998b, 1998c, and 1989]. Also considered were references provided in the USEPA Great Lakes Water Quality Initiative Technical Support Document for Wildlife Criteria [USEPA 1995a, pp.11-12] and the work of Sample et al. [1996].

For mammalian tests, defining tests that are greater than 10% of the test organism's life span as chronic is consistent with USEPA regulations for conducting toxicity studies under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and TSCA. Exposure during a sensitive life stage (e.g., gestation and embryo development) is considered a reasonable criterion to classify a test as chronic because of the potential for impaired reproduction and development. This is consistent with the method of Sample et al. [1996]. For subchronic mammalian tests, the USEPA defines a 90-day exposure duration as a standard for mice and rats, yet describes those exposures as approximately 10% of the life span of the animal [USEPA 1998b and 1998c]. Tests that are single exposures of extremely short duration (< 14 days) are considered acute.

c. The effect levels in the study should be those most clearly associated with no-to-low adverse effects. The type of effect levels that satisfy this criterion are--

    (1) No-observable-adverse-effect-level **(NOAEL).**

    (2) Lowest-observable-adverse-effect-level **(LOAEL).**

    (3) Effect Dose **(Ed_x)**, where x is less than 50.

The effect levels most useful for an ERA are those at the low end of the dose-response function.

d. The exposure pathway in the study most closely matches the pathway that will contribute the most to the exposure in the field. This will be a professional judgment

determination. For example, for oral exposures a feeding study may be preferred to a gavage study if the dose in food was well characterized and more applicable to the exposure route and matrix in the field.

e. The overall validity of the study design (e.g., exposure conditions and chemical form) relative to the appropriate exposure pathways in the environment will ensure the best possible toxicological risk estimate.

f. The quality of the study must be assessed and determined to meet general, minimal requirements appropriate for inclusion. Criteria that must be considered include--

(1) The variability in response (i.e., power of the statistical comparisons) must be assessed to be relevant and par to other studies considered for a specific substance and class of vertebrates.

(2) Bioavailability of the substance in the field and the one used in the toxicity studies must be comparable.

(3) Dose (administered) was quantified appropriately with a minimal amount of variability.

(4) Repeatability of study. Sufficient information must be presented to allow for a given study and its results to be repeated.

(5) Corroboration with other similar data.

A statement that describes the quality of all included relevant studies (or minimal criteria) should be presented in the toxicity profile after a characterization of effects, yet before the table or scatter diagram is completed.

The final step during relevant study identification is to determine if the relevant studies collected provide the data necessary to meet the minimum data set requirement. The minimum data requirements are—

- Data exist from at least three studies of sufficient quality to be deemed relevant (using the above criteria) which collectively provide data for three or more species within the taxonomic class.
- Data exist for at least two different taxonomic orders.
- At least two chronic LOAELs and at least one chronic NOAEL are available.

These minimum data set requirements for test organisms is consistent with the number of species required for the certification of substances for Food and Drug Administration (FDA) approval for human applications [FDA 1966]. Given the current state of the toxicological database, and the general variation in toxic response between species within a class, these requirements are considered reasonable. The minimum requirement for endpoint selection is based on professional judgment and experience with the literature. Section 2.4.4 discusses procedures for dealing with cases where the minimum data requirements are not met.

2.3 The Toxicity Profile

The toxicity profile is the written documentation of the collected information regarding the toxicological characteristics of the chemical(s) of interest before the selection or development of the TRVs. The toxicity profile must be designed to provide all the necessary documentation needed for the final TRV report to be clear and transparent. This is needed in order to defend risk management decisions.

A toxicity profile consists of two components:

a. Documentation of the literature search and how the relevant studies were selected.

b. Presentation of the data relevant to the development of TRVs (including a table and a scatter diagram of effects).

The toxicity profile should summarize the basic physicochemical characteristics of the chemical(s) and basic environmental fate and transport information. Such information is useful for the understanding of the potential exposure and toxicity of the chemical(s).

The documentation of the data collection and literature search should include—

a. The dates of the search.

b. A description of the search strategy used (including key words for computer searches) and the results.

c. An account of the relevant references obtained from which information was collected.

d. A listing of the literature sources actually reviewed.

The main portion of the profile should be the presentation of the available toxicity data. The extent of the discussion should provide all the information known about the nature of exposure and toxicity that is necessary for a risk assessor to understand the general characteristics of the chemical(s), yet be limited in scope (e.g., identify major target organs and endpoints, including details of the method of exposure, but not necessarily effects at higher exposures to non-target tissues). Major sources of information and data should be cited.

Major section headings should be organized first by class (e.g., mammals), then by route of exposure (e.g., oral, inhalation, dermal), and then by exposure duration (acute, subchronic, chronic). Exceptions can be made for appropriate mesocosm/microcosm or field studies.

All studies identified as relevant to the development of TRVs must be identified, and the rationale for their selection must be documented. The documentation should include a presentation of how each study satisfies the criteria used to identify them as relevant. The rationale behind the selection of particular studies and data to be used to develop TRVs needs to be documented so that it can stand up to peer review. Also, a discussion should be included summarizing the relevance of the available data with regard to population-level effects.

The profile shall include a scatter diagram that presents the quantitative data in the relevant studies specific to each taxonomic class. The scatter diagram will contain all reliable data regarding a specific route of exposure (e.g., oral), categorized based on endpoint (e.g., mortality, reproductive, developmental, systemic, and behavioral). Each data point presented in the scatter diagram will also be presented in table format including toxic endpoint, species, concentration and reference. All test species will be identified, as well as the effect levels (e.g., NOAELs and LOAELs). The scatter diagram approach is one of the best ways to summarize the data relevant to the development of TRVs. In this type of graphical representation, patterns of variability among species, endpoints, and exposure can be clearly evaluated.

To be consistent, the form and appearance of this presentation should generally follow the example provided in Appendix C.

2.4 TRV Derivation

At this point in the process, the toxicity profile is completed and all of the available data within a taxonomic class that are relevant to the development of TRVs have been presented. The toxicity profile will provide data that can be used to develop TRVs that will be protective of the entire taxonomic class and, in some cases, TRVs that are more specific to a **guild association**.

The USACHPPM Wildlife TRV Report will develop TRVs for each taxonomic class where sufficient data exists. Such class-specific TRVs are most useful as screening-level tools. This will allow project-specific screening-level assessments to be conducted with limited data analysis. In order to proceed through the ERA process with limited resources, the screening approach is suggested as a way to feasibly evaluate the potential hazards of many substances in an efficient manner [USACE 1996, Tri-Services 1996, and USEPA 1997 and 1998]. This approach helps to reduce the generally long list of potential chemicals of concern at many sites to a more manageable list. It is biased to support decision criteria requiring a high level of confidence to determine whether or not to further investigate potential risks.

When more site-specific TRVs are needed for a particular project (i.e., TRVs for a guild association or particular species), the data provided in the toxicity profile section of the wildlife TRV report should be used to develop such a TRV, if the appropriate data are available. Depending upon available resources, each wildlife TRV report produced by USACHPPM may provide one or more guild association TRVs in addition to the class-specific TRVs. The Standard Practice does not result in species-specific TRVs that may be needed for some assessments (see Sample and Arneal 1999 for an approach based upon **allometry**).

2.4.1 TRV Development Approaches

The available data (as documented in the toxicity profile) will determine which of the three following procedures are to be used. Regardless of the procedure, two TRVs are developed for use—a low and a high. A bracketed range provides the risk assessor with a level of confidence between which no observed adverse effects may occur and where low adverse effects may occur. It also allows for flexibility while considering the magnitude of uncertainty by not defining a bright line threshold. A range can be used to discriminate the relative importance of exposures that exceed the low TRV (e.g., when the HQ > 1). Although procedurally different, this concept is based on the collaborative work of the U.S. Navy, USEPA Region 9, California EPA, and others [PRC 1997].

a. Benchmark dose approach. Data that show a clear dose/response relationship in a unimodal design are best used to derive two TRVs based on the benchmark dose approach.

b. NOAEL/LOAEL approach. Data that do not have clear dose response relationships within well-designed and conducted parameters should be used to derive two TRVs, one based on an NOAEL and one based on an LOAEL.

c. Approximation approach. Where data are scarce and cannot be used for the aforementioned procedures, then the second approach will be approximated with the use of **uncertainty factors** (UFs) to derive TRVs that estimate an NOAEL and/or an LOAEL.

Each of these approaches describes development of pathway-specific toxicity values that can be used to evaluate an exposure consistent with the pathway of interest. For some organisms (e.g., terrestrial amphibians or pulse-feeding reptiles), a pathway-specific exposure TRV may not be appropriate since total exposure to the media would best describe exposure and would most likely be represented in the literature. In these cases, media concentrations (i.e., soil concentrations) can be derived using the same logic presented in each of the above procedures.

2.4.2 Benchmark Dose Approach

The benchmark dose approach uses the dose response curve to select the dose that corresponds to a 10% response (the ED_{10} or benchmark dose) and a dose that corresponds to the lower bound on the ED_{10} (the LED_{10}; based on the lower 95% confidence limit). These two doses (the ED_{10} and the LED_{10}) are then selected as the TRVs.

The benchmark dose represents the dose level that is associated with the effect level of concern. Since the precise shape of the dose/response relationship is critical at low estimates (Moore and Caux 1997), a 10% benchmark response is recommended as the "threshold for adverse effects" [USEPA 1998 and 1997] for the assessment endpoint. This infers that there is a 90% chance that no adverse effects will occur at exposures at the specified daily intake levels. The benchmark dose should ultimately be defined as an effective dose (e.g., ED_{10}) on the dose-response curve where, if exposures exceed the dose, it is suspected that adverse changes in the assessment endpoint will begin to become unacceptable. In this procedure, a study is chosen from those determined relevant based on endpoint, design, model, and overall quality. The endpoint selection should be one that is either suggestive of a population-relevant endpoint (see Section 2.2) or, when that is not known, is protective of the other endpoints.

The use of this approach is expected if available toxicological data can support it (i.e., if the data from the relevant studies identified in the toxicity profile can be used to develop a reasonable dose response curve). The curve should be developed using methods that are consistent with the current regulatory guidance on developing dose response curves and benchmark doses for use in risk assessment [USEPA 1995b] and the Benchmark Dose Software (BMDS, currently version 1.2) available from the USEPA National Center for Environmental Assessment found at the following address: www.epa.gov/ncea/bmds.htm.

The USEPA states that the "advantages of curve-fitting approaches include using all of the available experimental data and the ability to interpolate to values other than the data points measured" [USEPA 1998, p.26876]. These curves are more defensible and more useful in predicting and communicating risk. The shape of the dose response curve can be used to determine the presence or absence of an effects threshold, to evaluate incremental risks, and used as input for effects models (e.g., demographic models) [USEPA 1998].

The disadvantages of using dose-response curves are that the number of data points needed to complete the analysis are often not available, it is time intensive, and it is not always practical for toxicants that have a complex dose response relationship [USEPA 1998]. If

sufficient and appropriate data exists, however, the USEPA guidance supports the use of this approach [USEPA 1998 and 1995b].

2.4.3 NOAEL/LOAEL Approach

This approach produces two TRVs for the wildlife group of interest: the LOAEL for the most sensitive and ecologically relevant endpoint and the NOAEL for that same endpoint. These TRVs will be selected from the scatter diagram provided in the toxicity profile.

When the minimum data set requirements are met (Section 2.2) for the wildlife group of interest, then the TRVs are chosen from the studies identified as relevant in the toxicity profile using the following procedure. Selections should be made or reviewed by a toxicologist familiar with the literature.

a. Choose the LOAEL-based TRV by selecting the lowest documented LOAEL that either is suggestive of a population-relevant endpoint (Section 2.2) or, when that is not known, the LOAEL that is protective of the other endpoints.

b. Choose the NOAEL-based TRV by selecting the highest NOAEL (that is lower than the selected LOAEL) within the same endpoint as the selected LOAEL. If an NOAEL from the same endpoint is unavailable, then the highest NOAEL (that is less than the selected LOAEL) within all relevant endpoints should be selected.

The use of the NOAEL and LOAEL in screening-level assessments is consistent with USEPA guidance [USEPA 1997]. Selecting the highest NOAEL that is less than the lowest LOAEL, assuming that both toxic endpoints are relevant, is consistent with USEPA guidance [USEPA 1997, pp. 1-10] and ensures against unnecessary overprotection (i.e., where the lowest possible NOAEL is selected).

Chronic effect levels should almost always be included; however, an acute or subchronic exposure period may include important toxicological endpoints for some species and may better represent interspecific sensitivities. If the exposure duration of concern in an ERA is not the chronic scenario, then the choice of the exposure duration for the selection of the TRV should be left to the professional judgment of the project toxicologist.

Deviations from this procedure are acceptable if the reported toxicity data are not consistent with other work (e.g., outlier data) or if the endpoints are of questionable ecological relevance (e.g., enzyme induction).

When the minimum data requirements are met, the toxicity profile and its scatter diagram represent all the available data within a class of animals (including sensitive species); therefore, no UFs are needed to modify the values in setting the TRVs. All relevant class-specific data for each substance (including sensitive species) would be included in the toxicity profile (e.g., all mammal data). This format allows the variability in the data to be used to determine the taxonomic differences in toxicity instead of ambiguous UFs. This approach is consistent with guiding principles of toxicity data extrapolation [Chapman et al. 1998].

If the minimum data requirements are not met for the wildlife group, then the approximation approach should be used to develop the TRVs.

2.4.4 Approximation Approach

If the minimum data requirements are not met, then this approach is used. When the data set requirements are not satisfied, it means that the available toxicity data are insufficient to characterize toxicity for a class of animals with the desired degree of certainty. Therefore, it becomes necessary to use UFs in the development of TRVs until more toxicity data are available.

In this approach, the most relevant study identified in the toxicity profile that is most reliable in terms of quality and applicability should be used to develop TRVs that approximate the NOAEL and LOAEL-based TRVs described previously. These TRVs are developed by dividing the effect level of interest by appropriate UFs where multiple UFs are multiplied before dividing.

Extrapolation from a single study or from data that are unreliable given an understanding of the design (e.g., power of the statistical comparisons) may be not be appropriate. Professional judgment by a toxicologist is recommended to determine if the development of TRV approximations from limited data are justified.

The UFs used to develop TRVs need to account for potential differences in response between species, and differences in response due to exposure duration (e.g., acute vs. chronic) and endpoint (e.g., lethality vs.

NOAEL). A general UF of 10 to protect against potential interspecies differences should be used for screening-level assessments.

The UFs in Table 1 should be used to account for differences in exposure duration and endpoint. Most of these factors are based on the work of Ford et al. [1992], and are also presented in the current Tri-Service guidelines [Tri-Services 1996]. The factor for the chronic LOAEL to chronic NOAEL conversion is 10, whereas Ford et al. [1992] would apply a factor of 5. The USEPA identifies an approach that would apply a factor of 10 [USEPA 1997, pp. 1-10], based on an evaluation by Dourson and Stara [1983]. Note that where Ford et al. [1992] uses a combined UF of 16 to account for interspecies variability, this procedure uses a UF of 10 (see paragraph above). The rationale behind this change is that Chapman et al. [1998] recommends that any particular factor used in extrapolation should be limited to an order of magnitude.

Table 1. Uncertainty factors accounting for differences in response due to exposure duration and endpoint

Type of data available	UF to approximate a TRV that is	
	NOAEL-based†	LOAEL-based*
Chronic NOAEL	1	na
Chronic LOAEL	10	1
Subchronic NOAEL	10	na
Subchronic LOAEL	20	4
Acute NOAEL	30	na
Acute LOAEL	50	10
LD50	100	20

(†) Ford et al. 1992, except for the chronic LOAEL
(*) The factors for approximating an LOAEL-based TRV are derived using the other factors, assuming the chronic LOAEL is 5 times the chronic NOAEL.
(na) not appropriate

These UFs may be updated as new or as class- or chemical-specific information becomes available.

2.5 Confidence Level Assignment

All measures of effect contain some degree of uncertainty. The data available to develop TRVs are usually limited and not equal in their ability to describe risk. An assigned level of confidence should be used to communicate this fact, as it can be helpful to risk assessors and risk managers in—

- Determining the accuracy of the risk estimate.
- Judging overall uncertainty.
- Deciding where to focus additional resources to increase certainty.

The purpose of this step is to ensure that a qualifying estimate of the reliability for each TRV is documented and available.

The confidence levels should be qualitative (high, medium, and low) estimates of accuracy in the toxicity estimates. They should be based on professional judgment reflecting the confidence that the toxicologist has that the TRV selected will be accurate in predicting benchmarks of toxicity. Factors considered may include the range of interspecific variation in response, completeness of the database, and overall quality of the experiments from which the conclusions were based.

This step is consistent with the methods used by the USEPA in RfD derivation in human health risk assessment applications.

2.6 The TRV Report

The wildlife TRV report for a chemical shall describe the derivation of the TRV that, at a minimum, shall consist of the following components:

a. Discussion of how the data were used to generate the TRVs.

b. Documentation of the rationale behind all decisions made in the development of the TRVs.

c. Documentation of the confidence associated with each measure.

APPENDIX A

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APPENDIX B

GLOSSARY

Allometry — The USEPA [1998, p. 26880] provides the following discussion: "Allometry is the study of change in the proportions of various parts of an organism as a consequence of growth and development. Processes that influence toxicokinetics (e.g., renal clearance, basal metabolic rate, and food consumption) tend to vary across species according to allometric scaling factors that can be expressed as a nonlinear function of body weight."

Demographic Rates — Demographic rates refer to survival rate, birth rate, death rate, dispersal rate (i.e., immigration and emigration), and recruitment rate.

ED_x Values — An effective dose (ED) is one that elicits a response in a percentage (x) of animals tested. For example, consider a test where 10 out of 100 animals experience reduced growth after they are exposed to chemical X at a concentration approximately equal to 25 units per day for their lifetime. This result, lifetime exposure of 25 units per day of chemical X, can be expressed as the ED_{10} for growth effects.

Endpoints — Adverse effects that are likely to occur in a terrestrial vertebrate as a result of exposure to a contaminant. These effects need to be considered in an ecological context where effects likely to alter reproductive performance (e.g., courtship, nest defense, etc.), subsequent reproductive success (e.g., mortality) or other factors (e.g., interspecific competition, dispersal) are important in the life history of the species, the population, or the community.

Guild or Guild Association — In a general sense, a guild (or guild association) is a group of species with similar functional roles within a community [Simberloff and Dayan 1991]. In this document, guild refers more specifically to a group of species that have similar foraging (i.e., feeding) behavior and are related taxonomically (currently defined as within the same class). The implicit assumptions are: (1) species with similar foraging behavior are likely to be exposed to chemicals in similar ways and (2) the more taxonomically related species are, the more similar they are in terms of sensitivity to a toxin. Guild associates are the individual species within a particular guild.

NOAEL and LOAEL — These are acronyms for two toxicological endpoints. The NOAEL (no-observed-adverse-effect-level) is a concentration associated with no observed adverse effects in the tested organisms. The LOAEL (lowest-observed-adverse-effect-level) is a concentration associated with the lowest observed level of adverse effects in the tested organism.

Reference Dose (RfD) — An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from an NOAEL, LOAEL, or benchmark dose, with UFs generally applied to reflect limitations of the data used. Generally used in USEPA's noncancer health assessments.

Taxonomy and Taxon — Taxonomy is the science of classification as applied to organisms. A taxon is any group of organisms to which any rank of taxonomic classification is applied. Taxonomic nomenclature are based on a hierarchy of phylogeny (or similarity) of groups. Examples include species, genus, family, order, class, and phylum.

Toxicological Data Extrapolation — The procedure that estimates dose-response relationships for organisms that have not or cannot be tested themselves. It entails the process of inferring toxicity characteristics from a set of empirical toxicity data for an organism or taxon to other organisms or taxons.

Toxicity Reference Value (TRV) — A chemical concentration expressed as an administered dose (e.g., oral, inhalation or dermal dose) or as a media concentration for terrestrial amphibians that is used in conjunction with an exposure prediction to estimate health hazard or ecological risk.

Uncertainty Factor (UF) — A numerical value used to adjust an estimate of toxicity or risk. It is an approach for dealing with uncertainty related to assessing chemical risks.

APPENDIX C

WILDLIFE TOXICITY ASSESSMENT REPORT FOR 2,4,6-TRINITROTOLUENE (SAMPLE DOCUMENT)