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Environmental Human Health Risk Assessment Toxicity Values

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Environmental Health Science and Engineering Directorate
Toxicology Directorate

Technical Guide 373 Support Webpages:

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https://phc.amedd.army.mil/topics/envirohealth/hrasm/Pages/TG373.aspx

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1. SUMMARY

1.1 Purpose

Human health chemical toxicity values are required for environmental health risk assessments conducted across several different program areas. This technical guide, written for health risk assessment professionals, provides them with an understanding of the standard protocols for choosing human health toxicity values from among the variety of those published. The protocols within this guide are not to be interpreted as rigid; health risk assessment professionals can deviate from the standard protocols when doing so is necessary and scientifically justified. This technical guide is broad in scope and applies to Army Public Health functional areas, the Army Installation Restoration Program (IRP), Force Health Protection (FHP), and Deployment Health. This guide might also be useful for the other Services, but it has not been specifically endorsed by them.

The primary purpose of this technical guide is to instruct readers in the proper selection of toxicity values from among those that have already been derived and are thus available for potential use. The specification of the methods used to derive toxicity values is beyond the scope of this technical guide.

NOTE: This document does not address toxicity values for use in industrial hygiene assessments or ecological risk assessments.

1.2 Abstract

Quantitative environmental health risk assessment of human exposure to chemicals combines numerical estimates of population exposure with numerical estimates of toxicity or toxic potency informed by the chemical's dose-response relationship. The combination of the two leads to estimates of health risk. Chemical toxicity values are numerical point estimates derived from dose-response information to reflect a threshold for toxic effect, below which exposure is either unlikely to result in significant harm or is deemed acceptable for specific risk estimation purposes. When sufficient scientific evidence exists, a chemical may have one or more toxicity values, including non-cancer toxicity values derived to reflect different exposure durations, and toxicity values reflecting lifetime cancer potency. Additionally, agencies may use different assumptions to derive numerical toxicity values for different purposes. The use of standard values facilitates consistency of common information across risk assessments and allows environmental investigations to focus mainly on generating quality estimates of site-specific health risks based on site-specific environmental exposure assessments and situationally-specific toxicity values, if needed. In some cases, a toxicity value may be considered unusable for quantitative risk assessment because it is not scientifically defensible.

A comprehensive and standardized process for the selection of appropriate toxicity values for environmental health risk assessment is needed because the appropriate selection of values for

some chemicals is not straightforward. For example, a federally endorsed toxicity value may not exist for a particular chemical being assessed. This technical guide provides guidance for selecting toxicity values for chemicals. It focuses on toxicity values relevant to military personnel and their beneficiaries, civilian employees, and the general public, all of whom may encounter chemical hazards at military environmental sites or due to past or ongoing military activities. This technical guide does not address traditional occupational exposure limits designed for worksite risk management applications. Rather, its use should assist risk assessors in making appropriate and consistent decisions when selecting toxicity values.

1.3 Recommendations

Army environmental health risk assessors should consider using the guidance and toxicity values generated by the protocols described in this technical guide unless site-specific conditions or risk management frameworks justify a deviation.

2. REFERENCES AND TERMS

Appendix A provides the references cited, and the Glossary provides a list of acronyms and terms.

3. BACKGROUND

3.1 Toxicity Values

Chemical toxicity values are numerical point estimates, generally derived from dose-response information, to reflect a threshold for toxic effect, below which exposure is either unlikely to result in significant harm or is deemed acceptable for specific risk estimation purposes.[1] Most toxicity values are quantitative expressions of either (1) the potency of a chemical to cause a specific health effect, or (2) an estimation of the threshold exposure level of a chemical that indicates an exposure below which no adverse effects are expected. The former are used for cancer risk assessment, and the latter are used for other types of health risk assessment (e.g., noncancer risk assessment). Some toxicity values reflect a toxic effect risk that is informative for specific risk management decisions.

There are several kinds of toxicity values. Usually, toxicity values are expressed as either an exposure concentration, exposure dose, or the probability of developing cancer (i.e., cancer potency estimate). Cancer potency estimates can take different forms but have often been provided as either slope or potency estimates or unit risk estimates. Slope and potency estimates indicate the increased risk of cancer resulting from a specified level of exposure, while unit risk estimates indicate the cancer risk associated with a specific concentration over a lifetime of exposure. In cases where a threshold for carcinogenicity has been determined,

[1] While most toxicity values are point estimates derived from dose-response relationships, there are cases where toxicity ranges are preferred, or where some values are not based on dose response analysis (e.g., those based on LOAELS without identified NOAELs).

cancer toxicity values may be labeled similarly to non-cancer values (e.g., as a cancer-based reference dose).

The values are often normalized to body weight and often expressed as a daily average exposure across a specified or assumed exposure duration. Non-cancer toxicity values are also typically based on an observed toxic endpoint and characterized by the target organ from which toxicity is observed. Toxicity values are usually associated with specific routes of chemical exposure (e.g., inhalation, ingestion, dermal contact, etc.). Risk assessment methods also use toxicity values that are specific to age groups of the exposed population, particularly children.

Toxicity values are derived following a robust review of available and relevant data. **Section 4** provides an overview of toxicological assessments.

3.2 Use of Toxicity Values in Environmental Health Risk Assessments

There are generally two ways in which to use toxicity values in environmental health risk assessments. One approach is to use them for a formal risk assessment whereby the assessment calculates site-specific risks or, for effects that have a threshold, exposure levels below which no adverse effects are expected. This approach is used to determine if potential population exposures associated with an environmental site are unacceptable and therefore require remediation or other risk management controls.

Another approach is to use toxicity values to back-calculate exposure concentrations in air, water, soil, or another medium that would be considered acceptable and thus would not lead to environmental health risks of concern. This approach is used to develop site remediation cleanup levels, risk-based screening levels, and air and water quality criteria or standards (e.g., water quality criteria). The general process for selecting toxicity values should not differ across these risk assessment approaches.

3.3 Use of Toxicity Values for Other Purposes

Sometimes, toxicity values are used outside of a specific risk assessment context, such as to rapidly assess the relative rank of chemical hazards risk. For example, chemicals with a higher slope factor can be considered more potent in their ability to cause cancer than chemicals with a lower slope factor. However, caution should be exercised since, for example, a chemical with a higher slope factor based on animal data may have additional “safety” provisions (e.g., using 99th-percentile human equivalencies for extrapolation) not present for a chemical whose slope factor is based on human data. This approach may render a chemical to appear more potent than another, when similar scientific uncertainty may actually be present. A toxicologist can provide proper guidance on the utility and potential problems associated with using toxicity values.

3.4 Army and DOD Policies and Guidance Relevant to Toxicity Values

The TG 373 provides technical guidance pursuant to the following Army administrative policy guidance (shown in order of applicability):

- Army Regulation 40-5, *Army Public Health Program* (DA 2020a)
- Army Regulation 200-1, *Environmental Protection and Enhancement* (DA 2010)
- Department of the Army Pamphlet 40-11, *Army Public Health Program* (DA 2020b)
- Army Regulation 11-35, *Deployment Occupational and Environmental Health Risk Management* (DA 2011)

A specific Army policy that addresses the selection of environmental health risk assessment toxicity values does not exist. The U.S. Army Corps of Engineers (USACE) risk assessment handbook (DA 1999) addresses toxicity value selection in broad terms. TG 373 provides more specific detail, is broader in scope, and clarifies particular details not found elsewhere.

Two DOD documents specifically address environmental health risk assessment toxicity values:

- DOD Manual (DOD-M) 4715.20, *Defense Environmental Restoration Program (DERP) Management* (DOD 2012a)
- DOD Instruction (DODI) 4715.18, *Emerging Chemicals* (DOD 2019)

Toxicity values for environmental restoration are addressed in DOD-M 4715.20 (see enclosure E, p.32, of the manual). Toxicity values for emerging chemicals (ECs) are addressed in DODI 4715.18, which applies to DOD activities and programs involving the development, production, use, storage, or release of chemicals and materials that can be considered to be emerging contaminants. The Instruction defines an emerging chemical as relevant to the DOD and characterized by a perceived or real threat to human health or the environment, and having new or changing toxicity values or new or changing human health or environmental regulatory standards. The principles that underlie both of these policy documents were derived from the field of environmental health risk assessment and toxicology and are thus applicable to nearly all Army environmental health risk assessments. This TG 373 adopts and further clarifies and implements those principles.

4. TOXICOLOGICAL ASSESSMENTS

Toxicologists perform toxicological assessments to assess the available data related to known and potential health effects of a chemical or group of chemicals and to describe dose-response relationships for the purpose of deriving one or more toxicity values for use in risk assessment. Toxicity assessments consist of two actions, hazard identification and dose-response assessment, which follow a systematic review of all relevant literature. If sufficient evidence exists, the dose-response assessment will yield toxicity values.

The determination of toxicity values is independent of the environmental health risk assessment process. This technical guide does not address how to identify health hazards or perform toxicity assessments *per se*; rather, it summarizes the primary content of toxicity assessments and what is required of those assessments to yield suitable values for risk assessment. One example that may serve as an introduction to understanding the content of a toxicological assessment can be found in the “Preamble to IRIS Toxicological Reviews” section of recent

assessments produced by the U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment (see EPA 2017 for an example).

4.1 Hazard Identification

Hazard identification is the determination of whether a particular chemical is or is not causally linked to particular health effects (NRC 1983).[2] This step of the toxicological assessment documents the examination of relevant information that determines whether a chemical is capable of causing specific adverse health effects in humans and under what circumstances this occurs. Available data are scrutinized to determine the range of potential adverse health effects. The types of health effects that can occur often depend upon the route of exposure (e.g., inhalation, oral, and dermal), the exposure media contacted, and the duration, frequency, and magnitude of exposure (dose/concentration). Hazard information used to identify health effects and mode of action (MOA) of a substance is derived from human epidemiological studies, animal studies, *in vitro* studies, case reports, and medical experiments.

Hazard assessment involves weight of evidence (WOE) evaluations. The WOE describes the strength of the scientific inferences that can be drawn from a given body of evidence (NRC 2009). A WOE approach is used to characterize the hazardous properties of chemicals by analyzing all relevant observational and experimental data. The most important aspect of weighing the evidence is determining the likelihood that a chemical is a human carcinogen and what other health effects it can cause (e.g., neurotoxicity, reproductive toxicity). In general, hazards assessments are a review of the WOE associated with the following broad categories of health effects:

- Acute toxicity
- Local (portal of entry) toxicity
- Chronic systemic effects (including cancer and other effects)

Chemicals can cause local and systemic effects. Local effects refer to those that occur at the site of first contact between the body and the toxicant, while systemic effects require absorption and distribution of a toxicant from its entry point to a distant site where toxic effects occur. For most substances, except highly reactive materials, systemic toxicity and carcinogenicity are the primary concerns (Klaassen 1996). The types of health effects that can occur often depend upon the route of exposure (e.g., inhalation, oral, dermal, ocular, and injection), the duration of exposure, and the level of exposure (dose/concentration). In general, environmental health risk assessments are concerned with longer-term, low-level chemical exposures whereby systemic toxicity is the primary concern. Acute effects and local toxicity tend to be an additional concern during short-term, higher-exposure scenarios, such as incidents that can occur at industrial workplaces. Chemicals can have a combination of acute effects, local effects and non-local systemic effects (to include cancer).

[2] This definition of “hazard identification” differs from others often used in risk management. This form of hazard identification is a toxicological one and focuses on recognizing the types of health effects (the hazards) that can result from a given exposure to a chemical. Other, non-toxicological, approaches to hazard identification focus on recognizing or detecting the environmental agents that can pose a risk to health (e.g., the chemicals present at a site represent the “hazards.”)

4.1.1 Acute Toxicity

Acute toxicity describes the occurrence of adverse health effects resulting from a single exposure, an exposure of less than 24 hours (EPA 2018), or one that is less than 14 days (ATSDR 2018). Examples include irritation, burns, and allergic reactions. There are instances where a single acute exposure can lead to long-term chronic effects, such as following severe organ damage or neuropathies (e.g., exposures to chemical agents). An evaluation of acute toxicity data should include the relationship, if any, between the exposure to the substance and the incidence and severity of all abnormalities, including behavioral and clinical abnormalities and the reversibility of observed abnormalities, and should include information on gross lesions, body weight changes, effects on mortality, and any other toxic effects.

4.1.2 Local (Portal of Entry) Toxicity

Local toxicity (portal of entry effects) following short-term exposure results from immediate corrosive, irritating, or poisonous properties of the particular chemical at the point of initial contact. Skin, eyes, lungs, and the gastrointestinal (GI) tract are the primary targets of topical, aerosol, inhalation, and oral exposures, respectively. Local toxicity is not limited to acute or short-term exposures but can occur over chronic exposure to a chemical substance, examples of which include contact dermatitis or other allergic reactions. The Agency for Toxic Substances and Disease Registry (ATSDR) and the EPA are among several organizations that provide guidance for assessment of dermal, inhalation, and oral toxicity, as well as the assessment of eye and skin irritants (see the ATSDR toxicological profiles website[3] or EPA 1998b-e, 2002a, 2003a).

4.1.3 Carcinogenicity

Cancer describes a subset of lesions of the disease neoplasia (Klaassen 1996). Carcinogenicity is evident in malignant tumors found in humans or laboratory animals exposed to a given agent or in tumors found after exposure to structural analogues to the compound under review (EPA 2005e). Various governmental authorities have generated WOE schemes for identifying and ranking what is known about a chemical's causal relationship with carcinogenicity. Cancer toxicity values should only be generated for chemicals for which there is evidence of a potential cancer risk. Thus, a chemical's assigned cancer WOE rank is a required piece of information for a health risk assessment involving cancer endpoints.

There is also concern for cancer risk to children, including early-life exposures that may result in the occurrence of cancer during childhood, and early-life exposures that may contribute to cancers later in life. Historically, the focus on cancer has been as a disease associated with aging, resulting from extended exposure duration with prolonged latency periods before the cancers appear. However, emerging literature demonstrates that exposures in animals early in life (i.e., transplacental or *in utero*, early postnatal, lactational) can result in the development of cancer. Thus, one element in extending analyses to children is to evaluate the extent to which exposures early in life would alter the incidence of cancers observed later in life, compared with

[3] https://www.atsdr.cdc.gov/toxprofiledocs/additional_resources.html/#Profile_Development

the incidence observed with adult-only exposures. Particular attention is paid to carcinogens known to cause mutations in DNA. Analysis supports the conclusion that there can be greater susceptibility to the development of tumors as a result of exposures to chemicals acting through a mutagenic MOA when the exposures occur in early life stages as compared with later life stages. The EPA provides supplemental guidance for the hazard assessment of mutagenic carcinogens when exposure occurs during early-life versus adulthood (EPA 2005e).

4.1.4 Noncarcinogenic Toxicity

Noncarcinogenic toxicity generally refers to the production of a broad range of adverse health effects other than cancer. Examples of these include organ damage, liver toxicity, reproductive effects, and neurotoxicity. Depending on dose level, a single chemical can elicit more than one systemic toxic effect. During hazard assessment, the health effects thought to be associated with exposure to the chemical in question are identified, as are the relevant dose levels when the effects begin to occur. Standardized WOE ranking schemes, analogous as those used for determining carcinogenic potential, are now being used more often in the evaluation of the noncancer health hazards of concern for a given chemical. When toxicological assessments are prepared, the available health effects data are often organized by a series of effect categories as shown in the bullets below. Exposure levels of concern that have been identified with each kind of effect are often tabulated or graphically displayed to identify critical effects. Critical effects are the first adverse effects, or their known prodromal effects, that occur as the dose rate increases. Toxicity values established by the dose-response assessment are designed to protect against the occurrence of the adverse critical effect(s) of a given chemical. The ATSDR, EPA, and World Health Organization (WHO) are among several organizations that provide guidance for assessment of neurotoxicity, reproductive toxicity, and developmental toxicity (see the ATSDR toxicological profiles website[3], EPA 1991, 1996a, and 1998a; and WHO 2012).

- Acute lethal effects
- Respiratory effects
- Cardiovascular effects
- GI effects
- Hematological effects
- Musculoskeletal effects
- Hepatic effects
- Renal effects
- Dermal effects
- Ocular effects
- Endocrine effects
- Body weight and Metabolic effects
- Immunological and Lymphoreticular effects
- Neurological effects
- Reproductive effects
- Developmental effects

4.2 Dose-Response Assessment

A dose-response assessment characterizes the relationship between exposure levels and the incidence of specific adverse health effect in humans. Dose-response assessments are generally chemical-specific and performed to derive toxicity values that can be used in health risk assessments. Dose-response assessments are derived for the population under study. Variability between populations and sensitive subpopulations is considered during value development using uncertainty factors that provide a conservative margin of protection. Refer to EPA 2002b, for example, for further information about how uncertainty factors are utilized.

The selection of the key study and the critical effect used in the derivation of a toxicity value should, in preferential order, consider human epidemiological information and then animal bioassay information. The key study is the study of sufficient quality from which the critical effect is identified. The critical effect is the adverse effect occurring at the lowest dose in the most sensitive target organ, and, if identified in an animal bioassay, in the most sensitive species that is characterized as having a dose-response for "critical" adverse effect. While some organizations may prefer the use of only one critical study for quantitative analysis, there is a recent trend to consider multiple studies and/or multiple endpoints that estimate similarly low toxicity values. Such an approach derives multiple potential toxicity values before the final value is chosen.

Quantitative environmental health risk assessments generally involve toxicity values for both cancer effects and noncancer effects (if carcinogenicity has been established). Values for inhalation and oral exposure routes are most typically required; however, values for dermal, ocular, or other exposures may be required for some risk assessments. Additionally, toxicity values for different exposure durations—acute and chronic exposures, for example—are required to assess different kinds of exposure scenarios. Values can be derived for the general population, which includes susceptible subpopulations, or values for specific subpopulations, such as emergency responders, can be derived for use in unique situations.

4.2.1 EPA Standard Toxicity Values

The definitions of the standard set of EPA-generated environmental health risk assessment toxicity values are provided below. Similar types of values are generated by other organizations (see Section 4.2.2).

- Reference Dose (RfD) – The RfD is defined by the EPA as "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 a No-Observable-Adverse-Effect Level (NOAEL), Lowest-Observable-Adverse-Effect Level (LOAEL), or benchmark dose (BMD), with uncertainty factors generally applied to reflect limitations of the data used" (EPA 1995, EPA 2012a). Chemical-specific RfD values can be generated for acute, short-term, longer-term, and chronic exposure durations (EPA 2002b).

- Reference Concentration (RfC) – The RfC is defined by the EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation 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 a NOAEL, LOAEL, or benchmark concentration (BMC), with uncertainty factors generally applied to reflect limitations of the data used" (EPA 2012a). Chemical-specific RfC values can be generated for acute, short-term, longer-term, and chronic exposure durations (EPA 2002b).

- Cancer Slope Factor (CSF) – The CSF is defined by the EPA as "an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime

exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100" (EPA 2012a).

- Unit Risk (UR) – The UR is defined by the EPA as "the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. The interpretation of unit risk would be as follows: if the unit risk is 2×10^{-6} per µg/L, then 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per liter of drinking water" (EPA 2012a).

The above definitions and the methods for their numerical derivation have been under re-examination by the EPA for some time (e.g., EPA 2002b). Scientific and risk management debates continue as to how best to improve these values; however, these definitions have not undergone the broad, substantive changes that would impact how Army environmental health risk assessments are conducted.

4.2.2 Alternative Toxicity Values

Organizations other than the EPA, such as the ATSDR, some U.S. states, other nations, and non-governmental organizations, also derive and publish toxicity values for environmental health risk assessment. Because the EPA does not publish values for all chemicals and exposure time frames that might be of concern, these other sources of values must be considered when environmental health risk assessments are conducted. While different agencies develop and publish alternative values whose names differ from those defined above, many of these values are directly analogous to the standard set of values. Variations in definitions and derivation methodologies may impact the relevance of alternative values for any given risk assessment. This technical guide is relevant to all related toxicity values regardless of the labels assigned by their proponent agency.

4.2.3 Derivation of Toxicity Values

Toxicity values are typically derived from dose-response assessments by toxicologists with support from other risk assessment professionals. The primary purpose of this technical guide is the selection of toxicity values from among those that have already been derived and are thus available for potential use. The specification of the methods used to derive toxicity values is beyond the scope of this technical guide. This technical guide deals with the proper use of toxicity values once they have been published or otherwise made available.

5. GUIDING PRINCIPLES FOR SELECTING TOXICITY VALUES

The procedures presented in this TG 373 are based on a set of principles that ensure that selected toxicity values are scientifically defensible and appropriate for use in environmental health risk assessments. Guiding principles for scientific defensibility of toxicity values are listed below and include those found in DODI 4715.18 (DOD 2019).

1. Parties involved in the risk assessment should seek to identify the best, or most scientifically defensible, toxicity value.

2. Selected toxicity values should be derived from transparent assessments that clearly identify the information used and how it was used to derive the value.

3. Selected toxicity values should be derived from assessments that have been externally and independently peer-reviewed, where reviewers and affiliations are identified. Assessments with more extensive peer review are preferred. Panel peer-reviews are considered preferable to letter peer-reviews.

4. Selected toxicity values should be derived from assessments that were completed with a previously promulgated and publicly available methodology. Methodologies that were externally peer-reviewed are preferred over those that were not externally peer-reviewed.

5. Selected toxicity values should be derived from assessments that consider the quality of studies used, including their statistical power or lack thereof to detect effects, corroborate data among pertinent studies, and make best use of all available science.

6. Selected toxicity values should be derived from assessments that are publicly available and accessible. There may be a further preference for toxicity assessments in which public comment (as well as, but not in lieu of, external peer review) was invited and considered.

7. Selected toxicity values should be consistent with the duration of human exposure under evaluation. For example, when an exposure of 2 years is assessed, a subchronic dose should be preferred over a chronic dose.

8. Selected toxicity values preferentially should be consistent with the route of human exposure under evaluation. For example, in general, when an inhalation exposure is assessed, an inhalation value should be preferred over use of an oral value that was extrapolated for an inhalation route value. However, the value preference should be informed by careful consideration of the methods used (e.g., default approaches vs. PBPK modeling of target tissue dose) and the quality and endpoint coverage of toxicity testing by each route.

9. While assessments using established methodologies to derive toxicity values should be preferred, the methodologies should also be informed by the current best scientific information and practices. New assessment methodologies should be peer-reviewed, provide reproducible results, and meet quality assurance and quality control requirements.

10. Toxicological assessments should search all sources of toxicological and human health information to ascertain the best available science and identify uncertainties. If gaps in

the science exist for chemicals of importance to the DOD, then recommendations should be made for additional studies to reduce uncertainty.

6. OVERARCHING PROTOCOL FOR TOXICITY VALUE SELECTION

6.1 Protocol

Risk assessment toxicity values should be selected using the procedures referenced within **Table 1**. The protocol is to use the table to identify the appropriate selection procedure after first defining the risk management context for the risk assessment, the exposure durations, and the populations under consideration. On that basis, the type of selection procedure needed for a risk assessment is identified in the specific procedural guidance in this technical guide. This protocol is applicable to nearly all kinds of Army environmental health risk assessments.

The procedures for the selection of toxicity values will differ based on the risk management context for the risk assessment and the following two factors: (1) the most relevant exposure period (duration) linked to an effect of concern and (2) the population that is at risk. Each of these factors is described briefly in the subsections following the table.

Table 1. Environmental Health Risk Assessment Toxicity Value Selection Protocol

<table>
<tr><th colspan="2" rowspan="2">Human Exposure Duration[a]</th><th colspan="3">Risk Management Context[b]</th></tr>
<tr><th>Garrison Operations and General Population Exposures</th><th>Training Operations</th><th>Deployment Operations</th></tr>
<tr><td>Chronic</td><td>More than 7 years (up to a lifetime)</td><td>Go to Section 7</td><td colspan="2">Not applicable</td></tr>
<tr><td>Longer-Term</td><td>Up to 7 years (more than 30 days)</td><td rowspan="3">Go to Section 8.1</td><td rowspan="3">Go to Section 8.2</td><td rowspan="3">Go to Section 8.3</td></tr>
<tr><td>Short-Term</td><td>Up to 30 days (more than 24 hours)</td></tr>
<tr><td>Acute</td><td>Up to 24 hours</td></tr>
</table>

Notes:

[a] Toxicity values should be chosen for the known, or assumed, exposure duration under evaluation. Single, intermittent, or repeated exposures during each of the defined durations can be assumed. These definitions are adopted from the toxicity values harmonization process initiated by the EPA (EPA 2002b, p.4-2). Note that toxicity values for longer durations are, by definition, also protective for shorter durations.

[b] Toxicity values should be based on health endpoints and risk levels that are relevant to the population under evaluation. Protective toxicity values are selected for normal garrison operations, and the general population and military families, which include more susceptible subpopulations. Use of less protective toxicity values may be acceptable and warranted for some military operations based on mission requirements. Such values inform military operational risk assessments that consider risks associated with greater exposures.

6.2 Exposure Duration

The first factor to consider when selecting toxicity values is the exposure duration that is relevant to the risk assessment. This factor is important because the length and timing of exposure can significantly alter the relationship between exposure and health response. The exposure duration categories shown in **Table 1** are based on the toxicity values harmonization process initiated by the EPA (EPA 2002b, p.4-2). Continuous or repeated exposures during each of the duration categories are usually assumed.

While human exposures are rarely continuous, there is no universal separation time—for any given chemical—at which an exposure changes from continuous to intermittent. The EPA defines an intermittent exposure as "…one in which there is no effect of one exposure on the effect of the next; this definition implies sufficient time for the chemical and its metabolites to clear the biological system before the subsequent exposure, that is, noncumulative pharmacokinetics" (EPA 2002b). The pharmacokinetics and clearance time of a chemical and its metabolites are generally specific to that chemical or chemical class.

For any given risk assessment, when there are concerns about whether exposure should be considered continuous or intermittent, toxicologists should be consulted in order to determine (contingent on chemical and toxicity) if the time away from exposure is sufficient to consider exposures as separate (i.e., intermittent and not cumulative). As a conservative default approach, treating periodic exposures as additive and cumulative (i.e., continuous) will allow an assessment to be performed using values that are protective of chronic effects. Refer to **Section 8** for additional discussion.

6.3 Risk Management Context

The second factor to consider when selecting toxicity values is the risk management context, which is usually driven by the location, activities, and exposure scenarios of the site under assessment. The context is based on the decisions to be made and the guiding framework that is informing the decision. For the purposes of TG 373, there are three contexts, as shown in **Table 1.** The risk management context also includes the populations that are under consideration in the risk assessment. These are important for two reasons. First, the locations and activities associated with the exposures dictate the types of decisions under consideration, thus affecting the kinds of toxicity values that are relevant and informative (e.g., civilian standards versus military exposure guidelines). Second, whether or not sensitive subpopulation groups are included can significantly influence which toxicity value is most appropriate for the risk assessment.

7. TOXICITY VALUE SELECTION PROCEDURES FOR CHRONIC EXPOSURES

Environmental health risk assessments often evaluate chronic exposure scenarios, many of which address lifetime exposures to chemicals. TG 373 adopts the EPA's definition of chronic exposures, i.e., exposures lasting more than 7 years (EPA 2002b), as described in the following paragraphs (and in **Table 1**).

Chronic exposure scenarios apply to risk assessments for exposures at garrison sites, whereby garrison populations (including military personnel, civilian employees, and military families) and the general public may be exposed. Chronic exposure scenarios do not apply to assessing exposures at military training sites or deployment sites due to the shorter length of time that specific populations would be exposed at those sites. While ongoing military operations can continue for 7 years or more, the continuous exposure duration of any given segment of the deployed population is normally less than 2 years due to deployment rotation schedules.

Toxicity values for evaluating chronic exposures for garrison populations and the general public are selected according to a specific decision-logic that uses a hierarchy of available values. The hierarchy is based on the same underlying guidance as that in DOD-M 4715.20 and DODI 4715.18 (DOD 2012a, 2009) but is expanded to provide additional detail. The hierarchy follows the general guidance established by the EPA for its Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, or “Superfund”) and Resource Conservation and Recovery Act (RCRA) hazardous waste programs, which are articulated by the EPA Office of Solid Waste and Emergency Response (OSWER Directive 9285.7-53) (EPA 2003b) and the EPA protocol for health risk assessments for combustion facilities (EPA 2005b).

7.1 Chronic Toxicity Value Selection Procedure Overview

Figure 1 presents the standard TG 373 procedure for selecting substance-specific chronic toxicity values. When followed, the procedure will identify the TG 373 “initial” toxicity values for a substance and identify gaps when a defensible value is unavailable. The identification of gaps assists in the prioritization of substances for toxicological assessment and analysis. Deviation from the standard procedure may be necessary in some cases. Such deviations should be well-documented and defended using the principles defined in **Section 5**.

7.2 Key Chronic Toxicity Value Selection Procedure Concepts

7.2.1 Source Hierarchy and Unusable Values

The TG 373 procedure adopts the same tiered hierarchy of values (Tiers 1, 2, and 3) that is recommended by DODI 4715.18 (DOD 2019), which itself was adopted from an EPA OSWER Directive 9285.7-53 (EPA 2003b). Implicit in the hierarchy approach is the acknowledgement that the level of defensibility of values varies from high defensibility (i.e., higher tiers) to lower defensibility (i.e., lower tiers).

In addition, the TG 373 procedure expands upon the hierarchy by providing criteria by which to identify unusable values for quantitative health risk assessment; i.e., those that are not scientifically defensible and therefore should not be used to quantify health risks or hazards. The procedure for identifying such values is described in **Section 7.3 Step 4A**.

7.2.2 DOD Published or Endorsed Sources

The TG 373 procedure sets the choice of preference among values to those that have been endorsed by DOD toxicologists. Several alternative toxicity values may be available for a given chemical for a specific exposure route. The selection of the best value for risk assessments should be based on the application of the principles of toxicity value selection (**Section 5**) and be documented in a citable report.

Army or DOD documents that present a comparative analysis of the alternative values and recommend a value should be used rather than the application of a strict hierarchy of values. This comparative approach implements the guidance found in DOD-M 4715.20 and DODI 4715.18 (DOD 2012a, 2019) and is compatible with the approach articulated by the Provisional Toxicity Values Paper published by the Environmental Council of the States (ECOS) and Department of Defense Sustainability Work Group (ECOS-DOD 2007).

7.3 Step-Wise Explanation of the Chronic Toxicity Value Selection Procedure

The procedural steps for selecting chronic toxicity values are listed below and illustrated in **Figure 1**. These steps are described in detail in the subparagraphs following the figure.

Step 1 – Identify Chemical and Toxicity Value Requirements
Step 2 – Select Tier 1 Values from EPA IRIS[4], if Available
Step 3 – Select Tier 2 Values from EPA PPRTV[5] Program, if Available
Step 4 – Identify Possible Tier 3 Values from All Published Sources, if Available
    Step 4A – Assess the Tier 3 Status of the Identified Values
    Step 4B – Identify Values as Not Usable for Risk Assessment
Step 5 – Decide on How to Handle Multiple Tier 3 Values
Step 6 – Development of a Comparative Analysis of Available Values
    Step 6A – Review Committee
    Step 6B – Revise and Publish Comparative Analysis
Step 7 – Consider Development of a New Value
Step 8 – Development of a New Value and Toxicity Assessment (if so decided)
    Step 8A – Obtain External Peer-Review
    Step 8B – Revise and Publish New Value
Step 9 – Incorporate any Hierarchy Exemptions into the Set of Values
Step 10 – Perform Extrapolations and Adjustments, as Appropriate
Step 11 – Review Key Values Associated with High-Stakes Decisions

[4] Integrated Risk Information System (IRIS)
[5] Provisional Peer Reviewed Toxicity Values (PPRTV). Note that PPRTV screening values are not Tier 2 values.

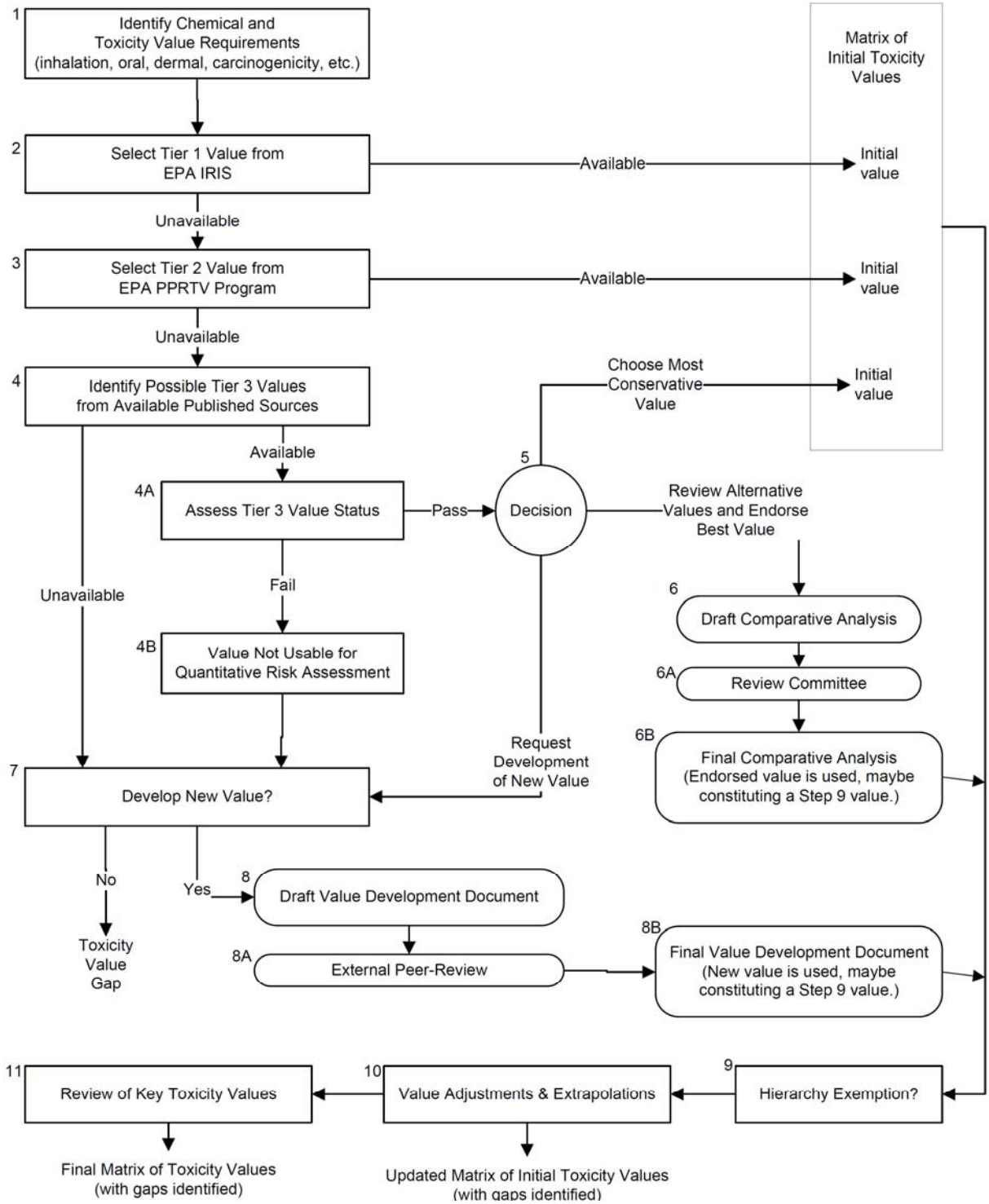

Figure 1. Chronic Toxicity Value Selection for Environmental Human Health Risk Assessment

7.3.1 Step 1 – Identify Chemical and Toxicity Value Requirements

Site (or source) information and the risk assessment conceptual model will identify the chemical substances, exposure routes, and population groups that will be evaluated. From this information, a data matrix can be constructed that identifies the number and kinds of toxicity values and supporting information needed to support the risk assessment. The following example illustrates this step.

Example:

Scenario. A risk assessment of a formerly contaminated area of soil must address exposures to natural resources personnel who will routinely work in the area during their normal outdoor duties. Assume that the area is near a supply barn, so routine contact in the area is likely, and that the assessment will need to evaluate chronic exposures because the workers will come into contact with the contaminated soil regularly over the course of their employment. Based on the conceptual site model, the routes of exposure are incidental oral ingestion of chemicals in soil, inhalation of chemicals in soil dust, inhalation of volatile chemical vapors from the soil, and direct dermal contact with soil. From site sampling data, the detected chemicals of concern are identified (as shown in **Table 2**).

Toxicity Values Requirements Matrix. The matrix in **Table 2** presents the required toxicity values for the risk assessment. Note that the carcinogenic WOE designation is sometimes desired when reporting the cancer slope factors (CSF) are needed for the assessment. After the WOE and CSF have been established (as applicable), the matrix should then be filled in according to the remaining toxicity value selection procedures.

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Table 2. Example Toxicity Value Requirements Matrix for Assessing Chronic Exposures

Chemical	Noncancer Values			Cancer Values*			
	RfC	**RfD_o**	**RfD_d**	**Cancer WOE Designation ****	**CSF_i**	**CSF_o**	**CSF_d**
Chemical A	✓	✓	✓	Carcinogenic to humans	✓	✓	✓
Chemical B	✓	✓	✓	A (Human carcinogen) (inhalation) D (Not classifiable) (oral)	✓	×	×
Chemical C	✓	✓	✓	B2 (Probable human carcinogen)	✓	✓	✓
Chemical D	✓	✓	✓	C (Possible human carcinogen)	✓	✓	✓
Chemical E	✓	✓	✓	Inadequate info to assess	×	×	×
Chemical F	✓	✓	✓	E (Evidence of non-carcinogenicity)	×	×	×
Chemical G	✓	✓	✓	Not yet assessed	×	×	×

Notes:

* Cancer unit risk values are often available when a slope factor is not. Such values can be converted to CSF values using these calculations:

$$CSF_o = [\ (UR_{water} * 1000\ \mu g/mg * 70\ kg)/2\ L/d\ ]$$

$$CSF_i = [\ (UR_{air} * 70\ kg * (1000\ \mu g/mg))/20\ m^3/d\ ]$$

Cautionary Note: Use of these equations may introduce unnecessary uncertainties into the risk calculations, compared to the direct use of the unit risks within some risk assessment calculations. If these equations are used, then the project toxicologist should be consulted as to the validity for the chemical and situation, as the limitations associated with extrapolating from a unit risk to a slope factor should be recognized. Note that the EPA does not recommend conversion between inhalation CSF and UR, instead relying on UR only for risk assessment (EPA 2005a).

** A cancer WOE designation may be helpful prior to knowing whether a cancer-based toxicity value is needed. The information presented in this example table provides potential designations retrieved from IRIS. There are also other sources of such designations, and the procedures defined herein discuss those. It is inappropriate to derive or use cancer toxicity values for chemical substances that have been determined to be non-carcinogenic, that have not yet been assessed, or that are not yet classifiable.

Legend:
✓ = Toxicity value that is required
× = Toxicity value that is not required
CSF = Cancer slope factor for inhalation (i), oral (o), or dermal (d) exposure ($mg/kg\text{-}d^{-1}$)
RfC = Reference concentration (for inhalation exposure) (mg/m^3)
RfD = Reference dose for oral ingestion (o) or dermal contact (d) (mg/kg-d)
WOE = Weight of evidence that the chemical causes cancer in humans

7.3.2 Step 2 – Select Tier 1 Values from EPA IRIS, if Available

For each chemical that is found in the online IRIS database, select the required toxicity values and the carcinogenic WOE designation(s) found in the toxicity values requirements matrix. If the required information is not available within IRIS, then move to the next step.

7.3.3 Step 3 – Select Tier 2 Values from EPA PPRTV Program, if Available

For each remaining toxicity value data requirement, select the PPRTV value and the carcinogenic WOE designation(s), if available (EPA 2008). For all remaining data needs, move to the next step.

CAUTION – The screening values occasionally found in the appendix of a PPRTV manuscript are NOT considered to be Tier 2 values. Rather, they are considered potential Tier 3 values and are assessed in the next step.

7.3.4 Step 4 – Identify Possible Tier 3 Values from All Published Sources, if Available

To fill any remaining gaps in the toxicity value matrix, identify all possible Tier 3 values published by other sources. If such values are identified, the process then moves to Step 4A where an assessment must be made as to whether the value(s) qualify as Tier 3. The absence of such values for a specific toxicity value requirement constitutes a potential toxicity value requirement gap, necessitating a decision on whether to develop a new value (go to Step 7).

- Step 4A – Assess Tier 3 Value Status

  After one or more possible Tier 3 values are identified, an assessment as to whether they qualify as Tier 3 values is necessary. **Section 7.4** provides the criteria used to identify Tier 3 values. Those values that meet the Tier 3 criteria are then considered Tier 3 values for possible use in quantitative risk assessment (go to Step 5). Those values that do not meet the Tier 3 criteria are classified as unusable for quantitative risk assessment (see Step 4B).

- Step 4B – Unusable Values

  Toxicity values that do not pass the minimum Tier 3 values criteria from step 4A should not be used in a quantitative risk assessment. (**Section 7.4** provides the criteria used to identify Tier 3 values.) Unusable values are too uncertain and do not meet minimum standards of scientific defensibility. Such values should not be used to support important risk management decisions.

  Values that are considered to be unusable for quantifying health risk according to this TG can be referred to as “screening” values. Screening values should not be used to quantify risk for the reasons stated above. In lieu of the availability of proper values for quantifying risk, the assessment team should qualitatively describe (but not quantify) the risk within the risk characterization phase of the health risk assessment.

7.3.5 Step 5 – Decision on How to Handle Multiple Tier 3 Values

At this point in the process, one or more Tier 3 values have been identified for possible selection as the toxicity value for risk assessment use. This step constitutes a decision point for the site-specific risk assessment team, whose decision options are as follows:

1. Select the most conservative value (or the only available value if that is the case),
2. Request a comparative analysis of the Tier 3 value(s) and an endorsement of the best value, or
3. Choose to initiate the development of a new toxicity value.

If option 1 is chosen, then the resulting value is labeled as the initial toxicity value for risk assessment use. Where multiple alternative values exist, the choice of the most conservative value as the toxicity value is generally appropriate when a comparative analysis is lacking. This choice is health protective and places an incentive on performing a formal review of the alternative values in order to identify the best value. The best value is not automatically the most conservative. When use of the most conservative value in a risk assessment does not trigger the need for a risk management decision (i.e., the health risk is found to be acceptable), there is no risk management imperative to use resources to review all the alternative values. Alternatively, when use of such a value may actually trigger a potential risk control action, it would then be appropriate to use resources to review how the selected value was derived and/or review all the alternative values to ensure that the risk control decision is based on the best and most scientifically defensible values available. In these review cases, it might be decided that a new value might need to be developed. High-consequence decisions might drive this type of outcome (refer to **Section 9** for more guidance related to such decisions).

If option 2 is chosen, then toxicologists will need to perform a comparative analysis that reviews the available Tier 3 values for the purpose of choosing the best one for use in quantitative HRA projects. Refer to Step 6 (**Section 7.3.6**).

If option 3 is chosen, then toxicologists can be tasked to develop a new value (see Step 7).

Note: Where multiple alternative values exist, a formal review should be accomplished to determine the best value. The best value is not automatically the most conservative value. If a comparative analysis is lacking and resources to complete such an analysis are not available, then in the interim the most conservative toxicity value is appropriate as a health protective choice.

As comparative analyses are performed and published, then the best values will be known and available for risk assessments and made available on the TG 373 support website.

7.3.6 Step 6 – Comparative Analysis of Available Values

Here, toxicologists review available alternative toxicity values for a chemical for the purpose of endorsing the best value for use in risk assessments. The comparative analysis should use the toxicity value selection principles presented in **Section 5** to make the determination. The priority should be given to those values that are based on the most current information, where the basis for the value is transparent and publicly available, and which have been peer-reviewed (see **Section 5** and EPA 2003b). The result of these reviews will be either an endorsement of a specific, previously published value or a recommendation to reassess the science and/or use newer analytical techniques with the data to develop a new toxicity value. Endorsements of values are more likely when available Tier 3 values have been published relatively recently; whereas, recommendations for new value development are more likely when sources of available values are older or where the importance of the chemical for DOD operations is high.

- Step 6A – Review Committee

  Prior to publication, the draft comparative analysis should be peer-reviewed by other DOD toxicologists. To accomplish this review, a committee should be established by canvasing toxicologists and health risk assessment subject matter experts across the Army and within the Tri-Service Toxicology Consortium, Tri-Service Environmental Health Risk Assessment Work Group, and the DOD Environmental Health Work Group.

- Step 6B – Revise and Publish Comparative Analysis

  After the draft comparative analysis is revised based on the findings of the review committee (see Step 9A), then the analysis should be published. It can then be used as a citable document within the TG 373 process.

7.3.7 Step 7 – Consider Development of a New Value

New values can be developed by toxicologists. If a new toxicity value is desired to support a risk assessment, then contact APHC or the appropriate Service Center and/or the Tri-Service Toxicology Consortium (TSTC) for assistance. This process takes time and should be reserved for situations that justify an investment of resources to perform the necessary data collection, analyses, and peer reviews required to publish a toxicity value that will be based on the principles articulated in **Section 5** and meet the Tier 3 value criteria (see **Section 7.4**). Newly developed toxicity values should be published as standalone reports that can be cited as Tier 3 values in Step 5 of this process.

Alternatively, non-DOD organizations can develop values and request their review and endorsement by DOD toxicologists, after which the determinations should be documented in citable reports. They can then be cited in Step 5 of this process.

In many cases involving assessments of more than one chemical exposure at a time, and depending on the purpose and scope of the project, risk assessments must proceed without fulfilling every single specific toxicity value requirement for all chemicals of concern due to the

time constraints associated with the decision making process. In other words, risk management decisions usually have to be based on incomplete information and knowledge. In these cases, the missing information must be acknowledged as an uncertainty in the risk assessment.

7.3.8 Step 8 – Development of a New Tier 3 Value

At this point in the process, a decision has been made for toxicologists to develop a new toxicity value. The resources required for value development will vary depending upon the available data and the complexity of the toxicology issues associated with the chemical(s) in question.

The new proposed toxicity value should be developed and documented within a toxicological assessment, as described in **Section 4**. Draft toxicity assessments are not appropriate for use until they have been peer-reviewed, the peer-review comments have been addressed in a revised draft, and the revised draft is available.

- Step 8A – External Peer-Review (Outside the DOD)

  After a draft toxicological assessment and proposed toxicity value are completed, an external peer-review of the documentation and analysis should occur. The outcome from the external peer-review process will be either (1) endorsement of the original value with few comments and no substantive comments, (2) substantive revision of the document and a revised value, or (3) a disagreement or lack of consensus on the assessment and/or the proposed value. In any case, a draft value cannot be considered a final value until the assessment and toxicity value have been peer-reviewed.

- Step 8B – Revise and Publish New Toxicity Value

  When the toxicological assessment has been completed and a final toxicity value has been derived and published in a citable document, the value should be publicly available so it can be cited for use during Step 5 of the TG 373 process.

7.3.9 Step 9 – Hierarchy Exemptions

This step is optional and is expected to apply in rare circumstances only. A chemical toxicity value will be considered to be in a hierarchy exemption status if one of the following conditions is present:

- One or more DOD published values compete with one or more Tier 1, 2, or 3 values, and a citable comparative analysis of the available values (see Step 6) endorsed a “best value” that is not the extant Tier 1 or Tier 2 value.

- No DOD published values exist, but the DOD endorsed a non-DOD value based on a citable comparative analysis that evaluated available values and endorsed a “best value” that is not the extant Tier 1 or Tier 2 value.

- A DOD entity recommends against the use of a specific Tier 1, Tier 2, or Tier 3 value for quantitative health risk assessment based on a citable analysis that evaluated the derivation of the value in question.

IMPORTANT: If a hierarchy exemption is under consideration, then coordination and collaboration with DOD, U.S. Government, and other stakeholders should occur to obtain necessary agreements and considerations.

7.3.10 Step 10 – Perform Extrapolations[6] and Adjustments, as Appropriate

At this point in the process, the toxicity value requirements matrix will be filled in with all of the initial toxicity values available (refer to the bottom of **Figure 1**). Additional toxicity values may need to be identified, such as age-dependent cancer slope factors (EPA 2005e) or dermal reference doses (RfD_d) via extrapolation from selected oral RfD values, as it is rare to find a published toxicity value derived specifically for dermal exposures (EPA 2004).

In this step of the process, acceptable techniques should be used for selection of age-dependent toxicity values and filling the remaining toxicity value requirement gaps. In summary, the following techniques can be used for implementing this step:

1. Basic route-to-route extrapolation, when appropriate;
2. Physiologically-based pharmacokinetic (PBPK) modeling; and
3. Carcinogens with a mutagen MOA and selection of age-dependent slope factors.

Some of the approaches for implementing each of the above techniques are described in **Appendix B** (Toxicity Value Extrapolations and Adjustments).

7.3.11 Step 11 – Review of Key Toxicity Values

The last step of the process, Step 11 generates the final matrix of toxicity values for a health risk assessment project. **Section 9** provides general guidance for performing a review of the key toxicity values that might drive risk assessment results and important risk management actions.

[6] Cautionary Note: Extrapolations may introduce unnecessary uncertainties into the risk calculations, compared to the use of directly derived values. If extrapolations or adjustments are used, then the project toxicologist should be consulted as to the validity for the chemical and situation, as the limitations associated with extrapolations should be recognized.

7.4 Evaluation Criteria for Identifying Tier 3 Values

To verify that an identified toxicity value is acceptable as a Tier 3 value, specific criteria need to be met. Implementation of the following criteria—which are considered minimum standards—will ensure that Tier 3 toxicity values meet basic standards of scientific defensibility and are therefore appropriate for use within quantitative health risk assessments. If any of these criteria are not met, the value should be considered to be unusable for quantitative risk assessment (see Step 4B).

1. A Tier 3 value is peer-reviewed. While it is preferable that a Tier 3 value be derived with an external peer-review, such as that for journal articles, reaching such a standard is not always possible. A value may be acceptable as a Tier 3 Value even if its derivation methodology has only undergone internal review for accuracy, especially if that is the only value that has been determined for that chemical. In cases where multiple values exist for a chemical, values from externally peer-reviewed articles or reports would be preferable. In cases where the source is a secondary source for the value, the primary source must meet the criterion, or the secondary source must be the peer-reviewing body.

2. A Tier 3 value is transparent, publicly available, and reproducible. “Publicly available” means that the data are available upon request but does not necessarily mean the data are immediately available from online sources. Documentation clearly describing the method and underlying studies used to derive a value is available to the stakeholders for review. Documents for limited distribution within a DOD organization are not transparent for traditional, civilian-type risk assessments and should be excluded from same.

3. A Tier 3 value’s derivation document preferably provides more than one substantiating study and includes a literature review. The studies utilized demonstrate sound science and have corroborating data among pertinent studies.

4. A Tier 3 value is not based on an underlying total uncertainty factor greater than 3,000. This statement is based upon guidance from an EPA RfD/RfC Technical Panel (EPA 2002b).

5. An exposure route extrapolation value, or a PBPK model-based value, is considered a Tier 3 value if the method of extrapolation is an acceptable method (see **Appendix B**). If the method of extrapolation is unavailable to reviewers or is unacceptable, then the value is not a Tier 3 value.

6. Where new approach methods (NAMs) are used to derive a toxicity value, an accepted, published approach or protocol should be used.[7] For read-across approaches, the EPA emphasizes structural, metabolism, and toxicity similarities (Wang 2012); other broader approaches have included bioavailability and toxicokinetics as well as considerations of uncertainty (Schultz 2015). In either case, an appropriate narrative weight-of-evidence regarding the choice of the surrogate chemical(s) should be provided. Additional considerations such as similarities in solubility (bioavailability), toxicokinetics, and

[7] NAMs can include read-across (analogue approach), high-content (transcriptomics, genomics, proteomics, etc.), and high-throughput methods (ToxCast/Tox 21).

toxicodynamics should be sufficiently accounted for, when applicable, to justify a potential Tier 3 value derived from read-across approaches. Finally, a statement of confidence and a discussion of uncertainty should accompany NAM read-across approaches.

NOTE: As of the time of this publication, the EPA PPRTVs that are designated as "screening" values do not qualify as quantitative Tier 3 values based on criterion number 6. For high-throughput or high-content NAM approaches, this criterion may have to be updated.

8. TOXICITY VALUE SELECTION PROCEDURES FOR LESS–THAN–CHRONIC EXPOSURES

Traditionally, environmental health risk assessments most often evaluate lifetime, or chronic, exposure scenarios. However, as health risk assessment and risk management practices have matured, risk assessment techniques for addressing less-than-lifetime exposures have become important for many kinds of health risk management decisions. For example, such risk assessments are useful for understanding short-term exposures during unique events associated with environmental sites or deployment environments, and for planning emergency responses to industrial accidents and other emergencies.

The less-than-lifetime exposure duration categories are identified as follows (from **Table 1**):

- Acute exposures last up to 24 hours.
- Short-term exposures last more than 24 hours and up to 30 days.
- Longer-term exposures last more than 30 days and up to 7 years.

When addressing less-than-lifetime exposure durations, it is sometimes important to consider situations associated with cumulative exposure for some chemicals. This occurs when repeated, less-than-lifetime exposures (contingent on chemical and toxicity) occur at the same location (or similar locations) over time when the time in between the exposures is insufficient (i.e., too short) to consider the exposures as separate (i.e., based on biological half-life data), thereby requiring the exposures to be characterized as cumulative and not intermittent. Potential chronic health effects can be a concern for some chemicals if the time between different exposure periods is insufficient for clearance of the chemical or if damage is persistent and/or cumulative. For example, lead is persistent in the body, and repeated exposures to elevated levels of lead may need to be considered cumulative. Alternatively, there are cases where short exposure periods are relevant to chronic health effects, such as developmental health effects. In these situations, toxicity values for less-than-chronic exposures should be designed to protect against such chronic effects.

For any given risk assessment, when there are concerns about whether exposure should be considered continuous or intermittent, toxicologists should be consulted in order to determine (contingent on chemical and toxicity) if the time away from exposure is sufficient to consider exposures as separate (i.e., intermittent and not cumulative). As a conservative default approach, treating periodic exposures as additive and cumulative (i.e., continuous) will allow an assessment to be performed using values that are protective of chronic effects because chronic

toxicity values are protective for less-than-chronic exposure. Such values may fit into the short-term or long-term exposure duration categories, depending on the duration of time the individual spends in a given location(s) with the same exposure risks.

8.1 Toxicity Values for Use at Garrison Sites

There is no one standard toxicity value selection procedure that covers all less-than-lifetime exposure durations associated with garrison activities addressing both military populations (e.g., military families) and the general population. Until a standard procedure exists, the recommended protocol is to consult with risk assessment subject matter experts at the APHC.

8.2 Toxicity Values for Use at Training Sites

Standard toxicity value selection procedures for assessments of exposures associated with military training site activities are not yet available. Until this technical guide is revised to include those procedures, the protocol is to consult with risk assessment subject matter experts at the APHC.

8.3 Toxicity Values for Use at Deployment Sites

Toxicity values have already been selected and used to derive military exposure guidelines (MEGs) for assessments of exposures at deployment sites. Technical Guide 230 (TG230), *Environmental Health Risk Assessment and Chemical Exposure Guidelines for Deployed Military Personnel* (USAPHC 2013), provides the MEGs and the process for using MEGs in generating a deployment risk assessment. The principles of toxicity value selection found in **Section 5** also apply to the process of value selection for MEGs.

9. REVIEW OF KEY TOXICITY VALUES FOR HIGH-STAKE DECISIONS

When the findings of a particular risk assessment have significant risk management implications, review of the key toxicity values within the assessment should be pursued prior to finalization of the risk assessment. Significant risk management implications include cases of site-specific critical situations and cases for which consequences exist for many sites or situations. Review consists of a consultation with toxicologists who can confirm the currency of the values used in the assessment and address any new information and analyses that may be relevant to supporting or refining the selected toxicity values.

Significant risk management implications can be varied but include those that relate to decisions with high resource or financial impact, decisions involving actual versus modelled exposures, decisions involving significant health risks, and/or decisions that may disrupt the community on an installation or adjacent to the installation.

In high-stakes decision-making, the level of uncertainty surrounding a key toxicity value should be considered an important factor. Toxicity value review may involve performance of a quantitative uncertainty analysis that incorporates using other published values. Uncertainty analysis cannot change the toxicity value; however, it can be used to derive a different toxicity

value based on different assumptions. Uncertainty analysis can allow for improved decisions informed by the uncertainty surrounding a given toxicity value.

10. DEVIATION FROM USE OF INITIAL TOXICITY VALUES

Some site-specific conditions or risk management frameworks may justify a deviation from the initial values. In most cases, environmental health risk assessments should use the toxicity values generated by the protocols described in this technical guide. This is especially important when time to complete the risk assessment is very short and additional resources are unavailable, thereby prolonging the analysis. However, for some chemicals of importance to the DOD, a DOD toxicology consensus on the most scientifically defensible toxicity value may not yet be available. If a specific risk management decision hinges upon one of these chemicals, then use of the TG 373 Initial Value in the risk assessment should be based on consultation with subject matter experts at the APHC (or another appropriate Service center).

11. TOXICITY VALUES FOR CHEMICAL MIXTURES

Evaluating exposures to specific mixtures, aside from pharmaceuticals and foods, has been used infrequently for site-specific environmental health risk assessment. Nearly all Army environmental health risk assessments performed at sites have adopted the basic EPA approach for site-specific risk assessments (EPA 1989): (1) adding the cancer risks of all known and possible carcinogens with CSF values into a single overall cancer risk estimate, and (2) adding the noncancer hazard quotients of all chemicals that share a common toxicity target organ or system. This strategy assumes additivity of similar effects and is generally considered a screening-level type of approach. Implementing this approach for estimating carcinogenic risk requires no additional information other than the exposure estimate and the toxicity value for each chemical substance. Implementing this approach for estimating noncancer toxicity target-specific hazard ratios requires the linking of each chemical-specific noncancer toxicity value to one or more toxicity target organs or systems.

More sophisticated approaches for mixtures risk assessment are available but have had limited use to date primarily because of scientific debate over the best methods. Nonetheless, some useful tools exist that allow more detailed assessments (i.e., EPA 1986b, 2000; ATSDR 2004, 2010). Additionally, the ATSDR has developed a series of Interaction Profiles for priority mixtures. These documents evaluate data on the toxicology of the “whole” priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health.

12. SUMMARY OF CHANGES

This is the first publication of TG 373. It should be revised if, over time, its content is determined to be inconsistent with evolving methodologies and/or regulations. Key changes made during revisions should be highlighted in this section.

APPENDIX A

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APPENDIX B

EXTRAPOLATIONS AND ADJUSTMENTS OF ENVIRONMENTAL TOXICITY VALUES

Contents

Tables

Note: References cited are included in Appendix A. Definitions of acronyms and terms are included in the Glossary.

B-1. PURPOSE

This appendix provides standardized methods for extrapolating and adjusting values in order to fill toxicity value requirement gaps that may be left after the initial data collection hierarchy has been completed. These methods are applicable for generating chronic exposure toxicity values and may not necessarily apply to the generation of less-than-chronic exposure toxicity values. The use of methods of extrapolation or adjustment other than those listed herein will generally not be favored as superior to the methods described in this appendix. As for any mathematical adjustment for deriving or adjusting a toxicity value, the method must be validated and supported by project toxicologists prior to its use in a health risk assessment.

B-2. ROUTE-TO-ROUTE EXTRAPOLATION

B-2.1 Introduction

"Route-to-route extrapolation" or "route extrapolation" refers to the practice of deriving a toxicity value for the desired route of exposure by extrapolating the toxicity value for another route of exposure. The preference is to avoid this practice and to derive toxicity values using data from studies of the same route of exposure evaluated in the risk assessment. In many situations, it is scientifically indefensible to perform route extrapolation. However, in certain limited circumstances, it can be defensible to use route extrapolation to temporarily fill in the missing toxicity values for a given route of exposure.

B-2.2 Background

Currently, very limited guidance on route-to-route extrapolation is available to risk assessors, who must, at times, obtain data from a single route of exposure. Most studies are carried out using the oral route (by gavage or in diet or drinking water) because such studies tend to be the most straightforward to perform and interpret, and dosimetry is easiest to quantify, particularly when a chemical is given by gavage (IGHRC 2006).[8] The chemicals for extrapolation should be considered on a case-by-case basis with expert judgment.

The use of route-to-route extrapolation is controversial because of its inherent uncertainties. Due to the increasing availability of Tier 3 toxicity values, the use of route-to-route extrapolation for certain situations has been limited or discontinued (e.g., oral-to-inhalation extrapolation). Section B-2.5 discusses these situations in detail.

Regulatory agencies have not often developed dermal toxicity values for assessing direct toxicity (i.e., portal-of-entry effects) and systemic toxicity via percutaneous absorption for chronic exposures to low-level concentrations of substances. For most substances, a scientifically defensible database for adjusting an oral toxicity value to estimate a dermal toxicity

[8] While precision of dose estimates results in toxicity values that appear to have less uncertainty, that precision is usually less important than the biological uncertainty that is introduced by using data from gavage experiments. The observed toxicities from gavage experiments have less relevance to human exposure patterns and potential human toxic effects that are not captured. Thus, the uncertainty for use in predicting or avoiding adverse effects is greater, though unquantifiable, with results from gavage experiments.

value does not exist. However, the U.S. Environmental Protection Agency (EPA) paradigm for making route-to-route (oral-to-dermal) extrapolations for selected substances (EPA 2004, 1989) can be used to derive interim values; refer to Section B-2.4.

B-2.3 Published Toxicity Values Based on Route Extrapolation

In some cases, the derivation of a published toxicity value is based on route-to-route extrapolation performed by the authoring organization. These types of toxicity values would be validated by the toxicity value selection process in Technical Guide (TG) 373, to include **Figure 1**.

As described in Section 5 of the main body of this document—

> "Selected toxicity values should be consistent with the route of human exposure under evaluation. For example, when an inhalation exposure is assessed, an inhalation value should be preferred over an oral value that was extrapolated for the inhalation route."

Therefore, when alternative published values exist for a given chemical and route of exposure, all else equal, there is a preference for not using the route extrapolated value.

B-2.4 Route Extrapolation for Developing Dermal Toxicity Values

Interim dermal toxicity values can be generated using the EPA paradigm for making route-to-route (oral-to-dermal) extrapolations for selected substances (EPA 2004, 1989). Dermal values are estimated by adjusting the oral toxicity values. Oral toxicity values are generally based on the level of chemical to which a test animal is exposed on a daily basis per unit body mass, rather than the amount of the dose that is absorbed into an animal's bloodstream. However, oral toxicity values based on an administered dose can be adjusted to account for this absorption by incorporating an estimate of the level of gastrointestinal (GI) absorption that is likely to occur after the chemical is administered. Equations 1 and 2 are used to calculate the dermal toxicity values; whereby, the caveats described above apply in the conversion of oral toxicity values to dermal equivalents.

$$RVN\text{-}C_d = RVN\text{-}C_o \times ABS_{GI} \quad \text{(Equation 1)}$$

$$RVC\text{-}C_d = \frac{RVC\text{-}C_o}{ABS_{GI}} \quad \text{(Equation 2)}$$

Where:
$RVN\text{-}C_d$ = Reference Value Noncancer Chronic Dermal (example units: mg/kg-d)
$RVN\text{-}C_o$ = Reference Value Noncancer Chronic Oral (example units: mg/kg-d)
ABS_{GI} = Fraction of the chemical absorbed through the gastrointestinal tract in test animals
$RVC\text{-}C_d$ = Reference Value Cancer Chronic Dermal [example units: $(mg/kg\text{-}d)^{-1}$]
$RVC\text{-}C_o$ = Reference Value Cancer Chronic Oral [example units: $(mg/kg\text{-}d)^{-1}$]

The current convention is to use an oral absorption estimate equal to 100 percent (ABS_{GI}=1) for those substances that, based on available data, have an oral absorption efficiency of 50 percent or greater (EPA 2004). The inherent variability in such data is great enough that unless the oral absorption efficiency is less than 50 percent, it is not considered significant enough to necessitate an adjustment to the oral toxicity value. The 100-percent assumption is also used for substances for which oral absorption data are not available. For substances whose oral absorption efficiency is less than 50 percent, the actual absorption estimate from an absorption (metabolism) study is used.

Notwithstanding the endorsement of the EPA, there are significant uncertainties associated with using this method to estimate dermal toxicity values. Dermal toxicity can be highly dependent on the route of entry (and not only for portal-of-entry effects: circulation and metabolism after systemic absorption from the skin can be very different from those of the GI tract). Accurate estimation of administered dose to the skin is problematic, and accurately estimating the absorbed dose from that administered dose compounds the uncertainty. In addition, any time an adjustment is made from the 100-percent absorption assumption of the oral toxicity value; the dermal value tends to be "more toxic" per unit dose.

The following table presents the current ABS_{GI} values for use in generating route-extrapolated dermal toxicity values for evaluating chronic exposures using the TG 373 process. Such values are to be generated during Step 6 of the process (see TG 373 **Section 7.3.6**).

Table B-1. GI Absorption Fractions (ABS_{GI}) used to Estimate Dermal Toxicity Values

Substance	ABS_{GI}	Source
Organic substances:		
Most organic substances (not otherwise identified)	1	EPA 2004*
Inorganic substances:		
All inorganic substances not listed	1	EPA 2004*
Antimony compounds	0.15	EPA 2004*
Barium	0.07	EPA 2004*
Beryllium compounds	0.007	EPA 2004*
Cadmium compounds (diet)	0.025	EPA 2004*
Cadmium compounds (water)	0.05	EPA 2004*
Chromium compounds	0.013	EPA 2004*
Chromium, trivalent	0.013	EPA 2004*
Chromium hexavalent ion	0.025	EPA 2004*
Manganese compounds	0.04	EPA 2004*
Mercuric chloride & other soluble salts	0.07	EPA 2004*
Nickel compounds	0.04	EPA 2004*
Silver compounds	0.04	EPA 2004*
Vanadium compounds	0.026	EPA 2004*

Note:
* EPA Superfund dermal guidance (EPA 2004, Exhibit 4-1).

B-2.5 Route Extrapolation for Developing Oral and Inhalation Toxicity Values

If no toxicity value is available for an oral or inhalation route, extrapolation may be used to fill data gaps. However, these situations will need to be evaluated on a chemical-by-chemical basis when a situation arises that requires such a value. A basic route extrapolation is not recommended. This analysis can be requested from DOD toxicologists. Doing so is analogous to requesting the development of a new Tier 3 value (step 7 in the TG 373 chronic toxicity value selection process). Situations will be handled on a case-by-case basis; however, DOD toxicologists may utilize new, sophisticated methodologies or may incorporate standardized, peer-reviewed practices of oral-to-inhalation or inhalation-to-oral extrapolations to generate a value (e.g., IGHRC 2006). Alternatively, a value developed externally may be submitted for endorsement to DOD toxicologists. In any situation in which a route-extrapolated value is used in an assessment, the uncertainty involved must be acknowledged.

B-3. PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELS

Physiologically Based Pharmacokinetic (PBPK) models are a computer-based approach for predicting internal doses at target organs, and are frequently applied to estimate toxicity values. These models are a “series of mathematical representations of biological tissues and physiological processes in the body that simulate the absorption, distribution, metabolism, and excretion of chemicals that enter the body” (EPA 2006). Models can be as simple as a one-compartment approach (instantaneous distribution) or up to multi-compartmental approaches, which take into account more processes such as tissue distribution, storage, etc. Application of PBPK models for dosimetry estimations can be undertaken by experts in the approach, and the type of approach taken is dependent on the exposure scenario and chemical of concern.

B-4. AGE-DEPENDENT CANCER SLOPE FACTORS AND CHEMICAL MUTAGENS

B-4.1 Introduction

In the assessment of childhood cancer risks, current EPA guidance recommends specific adjustments to how risks are calculated for those chemicals that are carcinogenic through a mutagenic mode of action (MOA) (EPA 2005c). This appendix provides the preferred approach to incorporating this methodology into Army risk assessments.

B-4.2 Background

The EPA’s 2005 Cancer Guidelines (EPA 2005c) emphasize using MOA in interpreting and quantifying potential cancer risk to humans. Evaluation of MOA plays a critical role in both the hazard identification and dose-response assessments. The EPA defines MOA as a “sequence of key events and process, starting with the interaction of a chemical with a cell, proceeding through functional and structural changes, and resulting in cancer formation” (EPA 2005c). The MOA describes how a chemical is absorbed, distributed, and metabolized to cause the onset of cancer.

EPA guidance recognizes that cancer risks for some chemicals are generally higher from early-life exposures than from exposures later in life. Early-life exposures may contribute to later-life effects. When carcinogens have a mutagenic MOA leading to such effects, the EPA guidance recommends that age-dependent adjustment factors (ADAFs) be used with selected cancer slope factors (CSFs) and age-specific estimates of exposure in the development of cancer risk estimates for several child age groups (i.e., < 2 years, 2 to 16 years, and 16 years and older). The default ADAFs are listed here:

- For age 0 to 2 years, the default ADAF is 10;
- For age 2 to 16 years, the default ADAF is 3; and
- For age 16 years and older, the default ADAF is 1.

B-4.3 Identification of Chemical Mutagens

Chemicals with a mutagenic MOA were initially identified by the EPA (EPA 2005c). Since 2005, the Agency has identified additional carcinogens that act via a mutagenic MOA. When the EPA publishes a cancer toxicity value for a chemical, the documentation might also indicate whether the Agency considers the chemical as having a mutagenic MOA. Otherwise, it is assumed that the chemical does not have a mutagenic MOA.

B-4.4 Use of Age-Dependent Adjustment Factors

The EPA guidance allows for deviations from the use of the default ADAF values in preference to the use of chemical-specific ADAF values (EPA 2005c).

B-4.4.1 ADAFs for Carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs)

Benzo(a)pyrene (BaP) is often used to assess cancer risks from other carcinogenic polycyclic aromatic hydrocarbons (PAHs). When this approach to assess early-life exposure for PAHs is used, the EPA recommends applying the ADAFs to the BaP slope factor before using the toxicity equivalence factors to estimate risk from other PAHs' exposure (EPA 2006).

B-4.4.2 ADAFs for Vinyl Chloride

The EPA does not recommend the use of default ADAFs for vinyl chloride. The EPA's IRIS toxicity profile for vinyl chloride recommends applying an uncertainty factor of 2 in the quantitative cancer risk estimates to account for the added risk from early-life exposure to vinyl chloride (EPA 2008a). The vinyl chloride CSF for exposure during adulthood is 0.72 $(mg/kg\text{-}day)^{-1}$. If exposure to vinyl chloride is continuous from birth, the twofold uncertainty factor should be applied so that the appropriate cancer slope factor becomes 1.4 $(mg/kg\text{-}day)^{-1}$.

B-4.5 Risk Assessment Approach

In accordance with the EPA guidance, this early-life approach should generally be implemented for site-specific risk assessment projects that anticipate child population exposure to one or more of these chemicals. This approach may require independent exposure assessments and

independent risk estimation calculations for each age group. However, the final decision for any given risk assessment should be based on consultations with subject matter experts and the risk assessment's stakeholders.

GLOSSARY

Acronyms/Abbreviations

µg/m3
Microgram per cubic meter

ACGIH
American Conference of Governmental Industrial Hygienists

ABSGI
Gastrointestinal absorption rate

ADP
Agent degradation product

ADAF
Age-dependent adjustment factor

APHC
U.S. Army Public Health Center

AR
Army Regulation

ATSDR
Agency for Toxic Substances and Disease Registry

BaP
Benzo(a)pyrene

BMC
Benchmark concentration

BMD
Benchmark dose*

CASRN
Chemical Abstract Service Registry Number*

CDC
Centers for Disease Control and Prevention

Note: Asterisks (*) identify terms that are further defined in the Glossary's Terms section.

CEPA
Canadian Environmental Protection Act

CERCLA or “Superfund”
Comprehensive Environmental Response, Compensation, and Liability Act

CIC
Carcinogen Identification Committee

CMRM
Chemical and Material Risk Management Directorate

CPF
Cancer potency factor (equivalent to CSF)

CSF
Cancer slope factor*

CSFd
Cancer slope factor for dermal exposures

CSFi
Cancer slope factor for inhalation exposures

CSFo
Cancer slope factor for oral ingestion exposures

CWA
Chemical warfare agent

DA
Department of the Army

DART
Developmental and Reproductive Toxicant Identification Committee

DERP
Defense Environmental Restoration Program

DOD
Department of Defense

EC
Emerging Chemical*

ECOS
Environmental Council of States

EPA
U.S. Environmental Protection Agency

FHP
Force Health Protection

FUDS
Formally Used Defense Sites

GI
Gastrointestinal

GPL
General Population Limit

HEAST
Health Effects Assessment Summary Tables

HESD
Health Effect Support Documents

HHBP
Human Health Benchmarks for Pesticides

IARC
International Agency for Research on Cancer

IRIS
Integrated Risk Information System*

IRP
Installation Restoration Program

ITER
International Toxicity Estimates for Risk

IUPAC
International Union of Pure and Applied Chemistry

IUR
Inhalation unit risk

LOAEL
Lowest-observable-adverse-effect level*

MEGs
Military exposure guidelines

mg/kg
Milligram per kilogram

MOA
Mode of action*

MOE
Margin of exposure

MRL
Minimal risk level

NAS
National Academies of Science

NOAEL
No-observable-adverse-effect level*

NSRL
No significant risk level

NTP
National Toxicology Program

OEHHA
Office of Environmental Health Hazard Assessment

OSHA
Occupational Safety and Health Administration

PAH
Polycyclic Aromatic Hydrocarbons

PCB
Polychlorinated biphenyl

PPRTV
Provisional peer-reviewed toxicity value

QSAR
Quantitative structure activity relationships

RCRA
Resource Conservation and Recovery Act

REL
Reference exposure levels

RfC
Reference concentration*

RfD
Reference dose; usually only refers criteria for oral ingestion exposures*

RfDd
Reference dose for dermal exposures

RfDi
Reference dose for inhalation exposures

RfDo
Reference dose for oral ingestion exposures

RoC
Report of Carcinogens

RPF
Relative potency factor

RVC
Reference Value Cancer

RVN
Reference Value Noncancer

SOP
Standard Operating Procedure

TCEQ
Texas Commission on Environmental Quality

TEF
Toxicity equivalence factor

TEQ
Toxicity equivalence

TERA
Toxicology Excellence for Risk Assessment

TG
Technical guide

TLV
Threshold Limit Value

TMF
Toxicity modifying factor

TTOS
Toxicity Target Organs and Systems

TV*
Toxicity value

UF
Uncertainty factor

URF
Unit risk factor*

URFa
Unit risk factor for air exposure

USACE
U.S. Army Corps of Engineers

USAPHC
U.S. Army Public Health Command

WOE
Weight of evidence*

Terms

Benchmark dose (BMD) or concentration (BMC)
A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response, or BMR) compared to background. [Source: EPA 2014]

Benchmark response (BMR)
An adverse effect, used to define a benchmark dose from which an RfD (or RfC) can be developed. The change in response rate over background of the BMR is usually in the range of 5-10%, which is the limit of responses typically observed in well-conducted animal experiments. [Source: EPA 2014]

Carcinogen
An agent capable of inducing cancer. [Source: EPA 2014]

Carcinogenesis
The origin or production of a benign or malignant tumor. The carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells. [Source: EPA 2014]

Chemical Abstract Service Registry Number (CASRN)
A unique numeric identifier designed to designate only one substance so it can be referenced by many Government Agencies and/or internationally. [Source: EPA 2014]

Chronic exposure
Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species). [Source: EPA 2014]

Dose-response assessment
A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence or change in level of response, percent response in groups of subjects (or populations), or the probability of occurrence or change in level of response within a population. [Source: EPA 2014]

Emerging chemicals
Chemicals relevant to the DOD that are characterized by a perceived or real threat to human health or the environment and that have new or changing toxicity values or new or changing human health or environmental regulatory standards. Changes may be due to new science discoveries, detection capabilities, or exposure pathways. [Source: DOD 2019]

Environmental Health Risk Assessment
A multi-disciplinary, science/policy methodology for measuring and managing health hazards found in the environment. Risk assessment deals with uncertainty and, therefore, is an iterative process by design. Any given health risk estimate is a product of exposure estimates, associated health effects, and uncertainty. They are designed to inform decisions and their generation is influenced by assumptions based on risk perceptions. The creation of a risk assessment product is an iterative process designed to be refined over several revisions until there is consensus on the most important and most uncertain factors affecting the results. How confident decision-makers need to be on these important but uncertain factors should drive the duration and complexity of the risk assessment life-cycle. [Source: this document.]

Hazard identification
The determination of whether a particular chemical is or is not causally linked to particular health effects. [Source: NRC 1983]

Health endpoint
An observable or measurable biological event used as an index to determine when a deviation in the normal function of the host has occurred. [Source: EPA 2007]

Inhalation unit risk
The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m3 in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10-6 per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical in 1 liter of drinking water. [Source: EPA 2014]

Lowest-observed-adverse-effect level (LOAEL)
The lowest exposure level at which there are biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group. [Source: EPA 2014]

Mode of action
A sequence of key events and process, starting with the interaction of a chemical with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation. [Source: EPA 2014]

Mutagen
A substance that can induce an alteration in the structure of DNA. [Source: EPA 2014]

No-observed-adverse-effect level (NOAEL)
The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control. Some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects. [Source: EPA 2014]

Oral slope factor
An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100. [Source: EPA 2014]

Reference concentration (RfC)
An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation 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 a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to

reflect limitations of the data used. Generally used in the EPA's noncancer health assessments. [Source: EPA 2014]

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. [Source: EPA 2014]

Reference value
Quantity value, generally accepted as having a suitably small measurement uncertainty, to be used as a basis for comparison with values of quantities of the same kind. [Source: *IUPAC Glossary of Terms Used in Toxicology, 2nd Edition.* Available at: http://sis.nlm.nih.gov/enviro/iupacglossary/glossaryr.html]

Risk management (in the context of human health)
A decision-making process that accounts for political, social, economic, and engineering implications together with risk-related information in order to develop, analyze, and compare management options and select the appropriate managerial response to a potential chronic health hazard. [Source: EPA 2014]

Slope factor
An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg-day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100. [Source: EPA 2014]

Toxicity assessment
Review of literature, results in toxicity tests, and data from field surveys regarding the toxicity of any given material to an appropriate receptor. [Source: EPA 2014]

Toxicity value
Numerical expression of a chemical dose-response relationship that is used in risk assessment (e.g., Reference Dose, Slope Factor). [Source: this document]

Uncertainty/variability factor (UFs)
One of several, generally tenfold, default factors used in operationally deriving the RfD and RfC from experimental data. The factors are intended to account for (1) variation in susceptibility among the members of the human population (i.e., inter-individual or intraspecies variability); (2) uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) uncertainty associated with extrapolation when the database is incomplete. [Source: EPA 2014]

Unit risk
The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m3 in air. The interpretation of unit risk would be as follows: if unit risk = 2 × 10-6 per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per liter of drinking water. [Source: EPA 2014]

Weight of evidence
An EPA classification system for characterizing the extent to which the available data indicate that an agent is a human carcinogen. [Source: EPA 2014]