EPA/600/R-18/224 | February 2018
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United States
Environmental Protection
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Standing Operating Procedure (SOP) for the Development of Provisional Advisory Levels (PALs) for Hazardous Chemicals

Office of Research and Development
Homeland Security Research Program

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Standing Operating Procedure (SOP) for the Development of Provisional Advisory Levels (PALs) for Hazardous Chemicals

Final

by

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IAG No. 1824- S870-T1
IAG No. DW-89-92241401
EP-W-12-026

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DISCLAIMER

The U.S. Environmental Protection Agency, through its Office of Research and Development, funded and managed the Provisional Advisory Levels project through two Interagency Agreements (IAGs): IAG No. 1824- S870-T1 with the U.S. Department of Energy (Oak Ridge National Laboratory; ORNL) and IAG No. DW-89-92241401 with the U.S. Environmental Protection Agency. ORNL is managed by UT-Battelle, LLC for the U.S. Department of Energy under contract DE-AC05-00OR22725. ORNL empaneled and consulted subject matter experts and was responsible for developing key work products, including the initial draft of this Standing Operating Procedure (SOP), which ORNL used to guide the development of Provisional Advisory Levels. An overview of the ORNL SOP document has been published as Young et al. (Inhalation Toxicology Volume 21, Supplement 3:1-11, 2009). Additional support was provided by CSS-Dynamac Corporation, through Contract EP-W-12-026.

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ABBREVIATIONS

ADJ ..... adjusted
AEGLs ..... Acute Exposure Guideline Levels
ATSDR ..... Agency for Toxic Substances and Disease Registry
BMC ..... benchmark concentration
BMCL ..... lower confidence limit of the BMC
BMD ..... benchmark dose
BMDL ..... lower confidence limit of the BMD
CAS RN® ..... Chemical Abstracts Service Registry Number
CEELs ..... Community Emergency Exposure Levels for Hazardous Substances
CFR ..... Code of Federal Regulations
DOE ..... Department of Energy
DTIC ..... Defense Technical Information Center
DWE ..... Drinking Water Equivalent
ERPG ..... Emergency Response Planning Guidelines™
HA ..... Health Advisory
HSDB ..... Hazardous Substances Data Bank
IDLH ..... immediately dangerous to life or health
IRIS ..... Integrated Risk Information System
LC_{50} ..... concentration lethal to 50% of the exposed group
LD_{50} ..... dose lethal to 50% of the exposed group
LOAEL ..... lowest observed adverse effect level
LOEL ..... lowest observed effect level
MF ..... modifying factor
MRL ..... Minimal Risk Level
NAC ..... National Advisory Committee
NHSRC ..... National Homeland Security Research Center (U.S. EPA)
NIOSH ..... National Institute for Occupational Safety and Health
NOAEC ..... no observed adverse effect concentration
NOAEL ..... no observed adverse effect level
NOEL ..... no observed effect level
NR ..... Not Recommended
NRC ..... National Research Council
NTIS ..... National Technical Information Service
OECD ..... Organization for Economic Co-operation and Development
PAL ..... Provisional Advisory Level

PBPK ..... physiologically-based pharmacokinetic
PELs..... permissible exposure limi
POD ..... point-of-departure
p-RfC ..... Provisional Inhalation Reference Concentration
p-RfD ..... Provisional Oral Reference Dose
QSAR..... quantitative structure activity relationship
RELs ..... recommended exposure limits
RfC..... Inhalation Reference Concentration
RfD ..... Oral Reference Dose
SOP..... Standing Operating Procedure
TD..... Toxicodynamic(s)
TEEL ..... Temporary Emergency Exposure Limit
TK..... Toxicokinetic(s)
TSCATS ..... Toxic Substances Control Act Submissions
TSD..... Technical Support Document
U.S. EPA..... U.S. Environmental Protection Agency
UF ..... uncertainty factor
UF_H ..... intraspecies uncertainty factor
UF_L ..... LOAEL to NOAEL uncertainty factor
UF_S..... severity adjustment uncertainty factor
UF_T ..... temporal extrapolation uncertainty factor

ACKNOWLEDGMENTS

The National Homeland Security Research Center is grateful to the staff and managers of Argonne National Laboratory and the Oak Ridge National Laboratory for dedicated and effective work, and to the members of the ONRL-assembled Expert Consultation Panel. Additional expert review of this document was provided by NHSRC's Cross-Agency Provisional Advisory Levels Steering Committee, comprising U.S. Environmental Protection Agency staff. Their guidance regarding technical approaches and strategic direction has been directly responsible for substantial improvements in these products. Technical and programmatic-minded scientists within and outside the Agency have provided valuable and far-reaching advice as Internal Technical Reviewers and as External Peer Reviewers. Their contributions are also gratefully acknowledged.

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1 Introduction

1.1 History/Project Context

Much of the nation's critical infrastructure can be subject to threats and intentional chemical, biological, or radiological attacks. Additionally, there is always the potential for releases of hazardous materials from accidents or natural disasters. The U.S. Environmental Protection Agency (U.S. EPA) aims to protect the public from the potential consequences of such incidents. Following the tragic results of the accidental release of methyl isocyanate in Bhopal, India, in 1984, increased attention was focused on the issue of anticipating accidental releases and preparing for such actions. In 1986, Congress passed the Superfund Amendments and Reauthorization Act (SARA), which contains provisions often referred to as the Emergency Planning and Community Right to Know Act. In response, the U.S. EPA developed a list of approximately 400 Extremely Hazardous Substances on the basis of their acute lethality information (U.S. EPA, 1987). Soon thereafter, the American Industrial Hygiene Association initiated its Emergency Response Planning Guidelines™ (ERPG) Committee, which began to develop one-hour inhalation exposure recommendations structured in a three-tiered system of severity addressing effects in a once in a lifetime exposure described as ranging from mild and transient effects, through serious or irreversible effects, to lethality (Rusch, 1993).

In 1991, the U.S. EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) requested that the National Research Council recommend guidelines for developing emergency exposure guidelines for exposures to hazardous substances. The National Research Council (NRC) released Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances (CEELs; NRC, 1993). The CEELs represent a tiered system of inhalation risk values targeted to emergency exposure durations of 1 to 8 hours, for exposures representing a once in a lifetime occurrence. These values address exposures that may produce effects ranging from discomfort, through those that may impair an ability to escape of produce disability, to life-threatening effects. The CEEL values were developed with a preference for human response data, from a relevant exposure duration.

To address the possibility of exposure to chemicals in use at Department of Energy (DOE) sites, and in the community in general, DOE embarked on a program to develop temporary exposure guidelines for chemicals not addressed by the CEEL or ERPG system. Early publications on the development of Temporary Emergency Exposure Limit (TEEL) values (Craig et al., 1992, Craig and Lux, 1998) reviewed available data and provided an overview of the development process for TEEL values, respectively. This led ultimately to the release of the DOE Handbook on Temporary Emergency Exposure Limits for Chemicals: Methods and Application (DOE, 2008). The TEELs are targeted to a 15-minute inhalation exposure duration and represent a tiered structure of risk values that are generally similar to those of ERPGs and later CEELs and Acute Exposure Guideline Levels (AEGLs). However, CEEL values also include a category 0 value, below which it is anticipated that no health risks will occur.

To reflect an expansion of coverage by these values to emergency planning, emergency response, incident prevention, and Superfund site remediation, NRC commissioned a new committee to develop Acute Exposure Guideline Levels (AEGLs; NRC, 2001). The resulting AEGL values were developed as a tiered system of inhalation risk values, which cover exposure durations from 10 minutes to 8 hours. The AEGL values are based on the tiered system for CEELs and the AEGL's tier-specific characterization of response was only minimally revised from that of CEELs. The primary difference is that the AEGL's Tier 2 was revised to specify that effects

would be serious and possibly irreversible, and expanded the definition to include effects that would impair the ability to escape, compared to the characterization in CEELs guidance as exposures producing a disability.

Recognizing that unanticipated chemical releases can also contaminate water supplies, the EPA's Office of Water develops Health Advisory (HA) values for multiple durations of exposure extending beyond one day. These values represent advisory, not regulatory, exposure values. Because the HA values are based on response types and response levels similar to those used to derive the oral reference dose (RfD), HA values approximate the same risk level. Both RfD values and HA values are based on toxicity data for effects occurring at relevant exposure durations: subchronic or chronic durations for RfD derivation, and one day, ten days, or lifetime (chronic) for HA derivation. HA value are disseminated as concentrations in drinking water (Drinking Water Equivalent Level values).

Because unanticipated chemical exposures may extend beyond 8 hours for inhaled substances and for durations between ten days and a lifetime for orally-encountered substances, the U.S. EPA's National Homeland Security Research Center (NHSRC) initiated the development of Provisional Advisory Levels (PALs) as a tiered system of health-based guideline values for oral and inhalation exposures of up to 24-hours, 30-days, and 90-days, and for other durations when necessary. (Figure 1).

Provisional Advisory Level (PAL) values are risk-based exposure guidance values for inhalation exposure and oral dosing. PALs have been developed for specified durations thought to represent those relevant to emergency response and emergency management scenarios. Figure 1, below, illustrates the relationship between PAL values and some other extant exposure standards and guideline values described above. Inhalation exposure guideline values include Acute Exposure Guideline Levels (AEGLs; NRC, 2001); Emergency Response Planning Guideline (ERPG; AIHA, 2016) values; and Temporary Emergency Exposure Levels (TEELs; DOE, 2008). These inhalation exposure guideline values cover exposures up to 8 hours. Inhalation exposure risk values (standards or legally enforceable limits) only address no-effect levels. Oral values are available for several durations, but only address no-effect levels. Inhalation Reference Concentration (RfC; U.S. EPA, 1994) values and Oral Reference Dose (RfD; U.S. EPA, 1993) values (which can be used to establish enforceable standards) and Minimal Risk Levels (MRL; ATSDR, 2017), an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure, address no-effect levels. Provisional Peer Reviewed Toxicity Values for Oral Reference Dose (p-RfD; U.S. EPA, 2017)) values; and Provisional Peer Reviewed Toxicity Values for Inhalation Reference Concentration (p-RfC; U.S. EPA, 2017) values are used to establish remediation goals for Superfund sites, and also address no-effect levels. So, unlike these existing guideline values and standards, PALs address inhalation exposure and oral dosing lasting longer than 8 hours and include human health effects ranging in severity from mild to lethal.

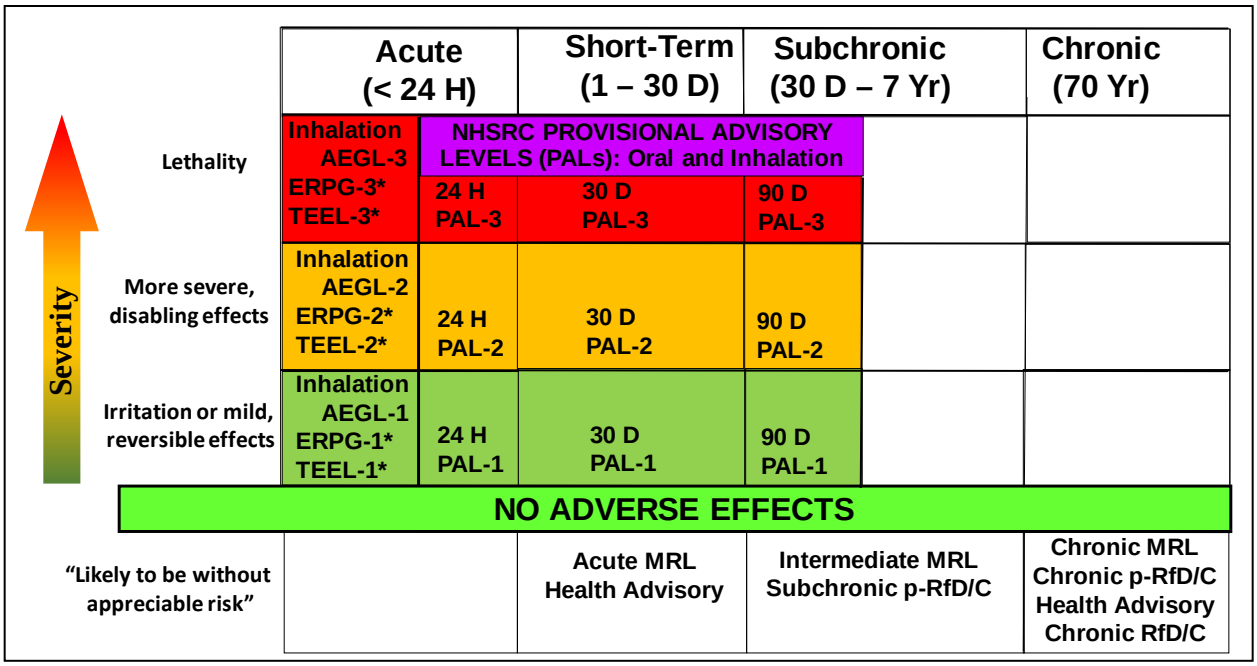

Figure 1. Exposure standards and guideline values.

1.2 General Scope and Application of PALs Program

Regulatory exposure standards have been developed for many chemicals to which human exposure can be anticipated or controlled. However, there are many chemicals for which regulatory exposure limits (standards) are not established, and/or for which exposure guideline values are not available. Further, regulatory exposure standards applicable to the general human (e.g., excluding OSHA PEL values for workers) population are seldom established for the durations of exposure relevant to activities undertaken during and following the unanticipated release of toxic chemicals as a result of accidental releases of chemicals, natural disasters, or terrorist activities. These situations may involve the release and subsequent exposure of limited or targeted segments of the general population to toxic industrial chemicals or chemical warfare agents. Adequate responses during and following these situations require making health-protective decisions as quickly as possible, based on the most reliable and appropriate information available.

PALs provide guidance to emergency response planners and those making response decisions at the federal, regional, state, and local levels by communicating the types and likelihood of health effects that are predicted to occur when exposures exceed those considered acceptable for the general population. Emergency situations are unique and often complex, including exposures that may vary over short time intervals and with respect to distance from the source, and including exposures to populations ranging from small groups of people whose composition may be well-defined or even controlled, to larger populations more broadly representative of the overall population and whose composition is not known. Management of emergency situations is not governed by any statutory exposure limits, and responsibility resides with on scene professionals who determine and direct emergency response operations and actions based on scenario-specific information. Like guidance values developed for other routes and durations of exposure, PALs guidance values can be used to inform (not determine) decisions for evacuation, re-use and re-entry into affected areas for specified durations. PALs values were

developed to extend the available suite of exposure guidance values by addressing exposure routes, durations, and health effects not covered by other risk value systems. Like guidance values developed for other routes and durations of dosing or exposure, PALs guidance values can be used to inform (not determine) decisions for evacuation, re-use, and re-entry into affected areas for specified durations.

PALs are *Provisional* because they represent conclusions drawn from a set of information that was current when summarized and because the exposure recommendations should be considered along with other pertinent information during the decision-making process. They are *Advisory* in that they are not regulatory values and are non-enforceable. PAL values are developed through risk assessment methods that are similar to methods to develop regulatory dose and exposure limits and dose and exposure values in other risk system that can/may/have been translated into regulatory limits and enforceable standards.

Like other inhalation guidance values represented by ERPGs, CEELs, TEELS, and AEGLs, PALs are structured as a tiered system of values, reflecting increasing severity of response in exposed individuals with increasing dose or concentration. The PALs severity scheme conforms to the first principle of toxicology – that response is a function of dose. Like AEGLs, PAL values are additionally structured by duration, with the important difference that PALs extend beyond the 8-hour duration of AEGLs to a 24-hr continuous exposure as well as up to 30 or 90 days. This aspect addresses another principle of toxicology – that duration of dosing or exposure also influences response.

Creating these tiers of risk values enables the identification of exposures that result in increased risks for the expression of more severe effects. Typically, tiers represent changes from baseline physiological parameters or mild and reversible effects; increasing to effects that are of an increased severity and are often irreversible, or are of a nature as to impede the ability to escape a contaminated environment; and increasing to morbidity, mortality, or life-threatening toxicity. Of course, the identification of irreversible, more severe toxicities involves a characterization of the responses that accompany higher oral doses or exposure concentrations. The description and characterization of such responses allows investigators to quantify the health impact (identify the human health condition and estimate the likelihood of its occurrence) and to identify medical countermeasures.

PALs are similar to Health Advisory (HA) values developed by the U.S. EPA Office of Water in that PALs and HAs are both advisory in nature, derived on the basis of toxicity or response information from relevant dosing or exposure durations, and are developed for less-than-lifetime exposures of defined durations. HA values "serve as the informal technical guidance for unregulated drinking water contaminants to assist federal, state, and local officials, and managers of public or community water systems in protecting public health as needed" (U.S. EPA, 2012a); their derivation has been described in some detail (Donohue and Lipscomb, 2002). Similarity also extends to RfD values with respect to the derivation and extrapolation of points of departure (POD). In these systems, it is expected that the effect characterizing the response under evaluation is not observed at the point of departure, as demonstrated in toxicity studies employing a dosing or exposure duration representative of the duration for which the risk value is developed. However, the PALs risk value system differs from these risk value systems (HA and RfD values) in the same way that PAL values are similar to the inhalation risk value systems described above (ERPGs, CEELs, TEELS, and AEGLs) – PALs address levels of severity greater than the no-adverse-effect level that serves as the basis for RfD and HA derivation.

Thus, three distinctions between PALs and RfD/ RfC values should be appreciated: the nature of the demarcation between response levels, the extent to which effects are characterized, and the duration of dosing or exposure covered. PALs are defined as *doses or exposures above which* the risk of responses characteristic of several levels of severity is expected to increase. In contrast, the oral Reference Dose or inhalation Reference Concentration is defined as, "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily dosing or exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988; US EPA, 1994; 2002). Operationally, RfD values are derived based on threshold doses for effects defined as "adverse," with the point of departure characterized as a NOAEL (no observed adverse effect level), a LOAEL (lowest observed adverse effect level), or a BMD (benchmark dose) value. The concept of "adverse" is inherent in the description of the reference dose relative to the "acceptable daily intake" (Barnes and Dourson, 1988), as well as reliance on a threshold for adversity (the "A" in NOAEL, LOAEL; e.g., preference for a NOAEL over a LOAEL as a point of departure value). Thus, oral RfD/inhalation RfC values are developed as doses or exposures anticipated to be without an appreciable risk of deleterious noncancer effects. In contrast, the likelihood of experiencing a given tier (severity) of effect is increased when dosing or exposures increase above a given PAL value. An important aspect of this circumstance is that PALs separate doses or exposures into those likely to produce three levels of severity, and identify the type of health effect likely to occur as dosing or exposures increase. Finally, PALs address durations of dosing or exposure representing durations pertinent to exposures during human activities during and following unanticipated chemical releases.

Situations that may benefit from the consideration of PAL values include, but are not limited to, transport/storage accidents, natural disasters, and subversive activities. PALs could be used in homeland security efforts, and by public health and law enforcement agencies, emergency response agencies, water utilities, EPA program and regional offices, and states and local governments. Like risk values for other routes and durations of dosing or exposure, PAL values represent a source of risk-based dosing or exposure values and describe a continuum of chemical-specific health effects possible with increasing inhalation concentrations or oral doses and increasing durations of exposure. This information may be useful to emergency planners as parameters for inclusion in the development of scenarios for potential events, where they may help inform the type and likelihood of injury and thereby support estimates of the consequences of an unanticipated release. The results can aid in decisions regarding medical countermeasures and evacuation requirements.

However, the primary application of PALs is to represent a source of information to guide decisions for reentry, resumed use, and protective action for the prescribed durations of exposure. Reentry is defined as the entry of persons into an affected area following a release. Resumed use refers to the reutilization of items and infrastructure impacted by a chemical release. Protective action is an action or measure taken to avoid or reduce dosing or exposure to a given hazard. In the event of a release of a chemical, recommendations for protective action could include shelter-in-place, use of personal protective equipment, evacuation, etc. Additionally, consideration must be given to selective use/reuse of resources; e.g., community water supplies not considered potable may be suitable for other uses.

This standing operating procedure (SOP) is intended for use by toxicologists and health risk assessors who are familiar with basic toxicological principles and health risk assessment methods.

1.3 The Technical Support Document

One Technical Support Document (TSD) should be developed per chemical or group of closely related chemicals (e.g., G nerve agents) for which a set of PAL values is determined. The TSD may contain introductory material such as that describing the history of emergency exposure value development, the intent of PAL values relative to the emergency preparedness and homeland security missions, and other programmatic information. An Executive Summary section should present information specific to the chemical sufficient to guide an understanding of the importance of oral dosing and inhalation exposure, primary manifestations of toxicity that may result from dosing or exposure, and the PAL values for the chemical. The remainder of the document should be organized into sections addressing the areas presented in the bulleted list below. These areas should be developed at a level of detail to convey their significance to the development of PAL values. The primary purpose of the TSD is to present information sufficient to provide an understanding of the development of a range of effects with respect to both dosing and exposure magnitude and duration, and to demonstrate a reliable estimation of the risk of those effects based on the available data, interpreted in accord with this SOP. The following list of topics should be given attention in the Technical Summary Document:

- Chemical identification
- Chemical/physical properties
- Environmental fate (air and water)
- Absorption, distribution, metabolism, elimination (ADME)
- Toxicokinetics/Toxicodynamics and Mechanism(s) of toxicity
- Susceptibility
- Human toxicity data
- Animal toxicity data
- Recommended PAL values and rationales
- Other guideline values
- Data gaps and needed additional research
- References

2 Definitions of PALs, PAL Tiers, and PAL Dosing or Exposure Durations

2.1 PALs

PALs are advisory levels relevant to concerns regarding possible dosing or exposure of the general public in emergency situations. As described above (Figure 1) PALs are developed to describe a tiered set of responses based upon health-based criteria appropriate for each health effect tier for a range of durations. Three tiers (PAL-1, PAL-2, and PAL-3), distinguished by the severity of toxic effects and are the same as those developed for AEGLs. The durations for PAL estimates should be based on emergency response needs. Recommended durations include up to 24 hours, up to 30 days, up to 90 days, for oral dosing or inhalation exposure, but the application of PALs methods to derive values for other durations may be justified based on emerging needs. There is no requirement to develop values for specific durations. The health effect for a given chemical (and route, duration and tier) is the biological effect identified by a specific data set and for which its relationship to oral dose or inhalation exposure has been defined. Although PALs

are developed with considerable attention to sensitive populations (e.g., asthmatics, age-dependent sensitivities), PALs are not intended to protect hypersensitive individuals or against idiosyncratic responses.

Definition of PAL Tiers:

PAL-1 represents the assumed, duration-specific continuous dosing level or exposure concentration of a chemical above which changes from a baseline of specific biomarkers or physiological responses could have adverse health effects in the general population. Concentrations at or below PAL-1 are not expected to be associated with adverse health effects. Increasingly greater concentrations above the PAL-1 value could cause progressively harmful effects in the general population, including all age groups and sensitive subpopulations.

PAL-2 represents the assumed, duration-specific continuous dosing level or exposure concentration of a chemical above which serious, possibly irreversible, or escape-impairing effects could result. Increasingly greater concentrations above the PAL-2 value could cause progressively harmful effects in the general population, including all age groups and sensitive subpopulations.

PAL-3 represents the assumed, duration-specific continuous dosing level or exposure concentration of a chemical above which lethality in the general population, including all age groups and sensitive subpopulations, could occur.

2.2 PAL Exposure Durations

The three PAL tiers (PAL-1, PAL-2, and PAL-3), distinguished by the degree of severity of toxic effects, may be developed for dosing or exposure durations of up to 24-hours, up to 30-days, up to 90-days, or other durations deemed relevant via oral and inhalation routes. Information previously compiled in other risk value systems should be consulted. For example, for inhalation exposure of less than 24 hours to chemicals, additional consultation of other risk values such as Acute Exposure Guideline Levels (AEGLs) or Emergency Response Planning Guideline (ERPG) values is recommended. AEGL values were developed by the National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) for many chemicals and are based upon a similar three-tier approach with careful attention being given to the concentration-time relationship for the exposure durations of concern (10 minutes, 30 minutes, and 1, 4, and 8 hours). ERPG values are developed by the Emergency Response Planning Committee of the American Industrial Hygiene Association using a similar three-tiered approach for chemicals in anticipation of a one-hour, once in a lifetime exposure. For oral exposures of 24 hours or less, information contained in EPA's Health Advisory and Human Health Benchmarks for Pesticides systems, as well as in ATSDR's Acute MRL values should be evaluated. Information in other risk systems pertinent to other PALs durations should also be considered (e.g., information in subchronic and chronic reference value derivations for longer-term PALs durations). The 30-day PAL will be applicable to durations of greater than 1 day to 30 days. The 90-day PAL will be applicable to durations greater than 30 days to 90 days. Values will be developed only if data describing the development of a tier-appropriate health effect from a duration-relevant experimental dosing or exposure duration is available. The relevance of an experimental dosing or exposure duration to the targeted PAL duration will be justified on the basis of duration-response information for the chemical, for the lesion(s) observed following the dosing or exposure to other chemicals, or on the basis of professional judgement. Additional information on temporal aspects of dosimetry is contained in sections 5.3.5 and 5.4.3.

3 PALs and Other Standards/Guidelines

While PAL values are uniquely structured to fill important gaps in available standards or guidelines for dosing or exposure values, information contained in some existing standards/guidelines may be useful in determining PALs. These standards/guidelines may include, but are not necessarily limited to, Drinking Water Health Advisories, p-RfCs and p-RfDs, RfCs and RfDs, NIOSH [National Institute for Occupational Safety and Health] RELs [recommended exposure limits], NIOSH immediately dangerous to life or health (IDLH) values, ATSDR MRLs (minimal risk levels), ERPGs, AEGLs, and military standards/guidelines. However, consideration must be given to the extent to which these standards and guidelines have been developed for broad or specific human populations, and the extent to which they are based on an intent (or mandate) to provide an extent of health protection as complete as possible.

Existing standard or guideline values or points of departure identified for their derivation may be used in the estimation of a PAL value, however, it is imperative to provide a rationale for their use. Standard or guideline values derived for relevant exposure durations, and based on relevant health endpoints will be the most valuable for consideration. Summary or support documents for other standard or guideline values might also contain data or information pertinent to PAL value determination (e.g., descriptions of more severe health effects occurring at shorter durations of dosing or exposure than those pertinent to the particular standard or guideline value being supported). Any quantitative adjustments and assumptions regarding the use of existing standards and guidelines should be clearly described on a case-by-case basis.

4 Data supporting PAL Development

4.1 Literature Search

Reliable literature describing key aspects related to chemical oral dosing or inhalation exposure and toxicity should be evaluated, whether available in the open and peer-reviewed literature, in reports from contractors or the government, or study summaries as available in some regulatory files. The focus of this task is on identifying reports describing toxic effects of the chemical, but should also include identification of important sources describing: chemical/physical properties, environmental fate (air and water), absorption, distribution, metabolism, elimination (ADME), toxicokinetics (TK) / toxicodynamics (TD) and mechanism of toxicity, and human susceptibility.

The goal of this task is to produce a comprehensive search of the literature for the researcher to identify and review. The specific approach is determined by the amount of information obtained on the chemical of interest during the initial search. The initial search should be based on a strategy including broad terms such as “toxicity,” chemical name, synonyms, and CAS RN® should be employed, and revised to include more terms descriptive of the effects known to be associated with the chemical, as necessary. When necessary, additional search iterations may be conducted based on additional information for the chemical including search terms more descriptive of the organs, tissues, processes, or systems affected. Ultimately, this process should identify and prioritize for retrieval studies that demonstrate a dose- or exposure-dependent effect of the chemical on living mammals exposed via the oral or inhalation routes.

In addition to sources of information that may be chemical- or program-specific, primary databases include TOXNET®, [TOXNET is a collection of six databases – HSDB, CHEM-ID, TOXLINE, CCRIS, DART, and GENETOX.] TOXLINE®, Hazardous Substances Data Bank (HSDB), PubMed®, Web of Science®, National Technical Information Service (NTIS),

Integrated Risk Information System (IRIS), Defense Technical Information Center (DTIC), NIOSHTIC-2, and the U.S. EPA Toxic Substances Control Act Submissions (TSCATS).

In some cases, reports from the non-peer-reviewed literature may be identified (e.g., industry internal reports, industry submissions to EPA offices, military research with limited distribution restrictions, or unpublished reports from other sources), and may present potentially valuable quantitative (i.e., dose or exposure response) information. In these instances, the reliability of the reports with respect to characterizing the dose response and identifying a point of departure for potential critical effects will be evaluated as part of the peer review for the respective Technical Summary Document. Section 4.2 provides additional guidance for study evaluation. For some chemicals (e.g., nerve agents, riot-control agents, lacrimators, and sternutators), data come from military sources. Only unclassified, non-confidential literature will be incorporated into PAL documentation, which then allows for the PAL documentation to be unclassified as well. The use of limited distribution information (a separate issue from classification) will be determined on a case by case basis. Some sources for such data include the Chemical, Biological, Radiological, and Nuclear Defense Information Analysis Center's on-line files, and reports from the U.S. Army's Edgewood Chemical Biological Center.

4.2 Study Evaluation and Selection

Many toxicity studies used as the basis for risk value development are not conducted according to regulatory guidelines or protocols for endpoint-specific evaluations. Their structure may demonstrate a basis on protocols developed to support different types of decisions or generate data useful for another purpose, they may employ different quantitative methods or statistical models than those prescribed elsewhere, and may communicate conclusions based on the information available to the authors at the time. Consequently, study reports should not be judged solely on the basis of currently accepted experimental protocol criteria; neither should the conclusions reached by study authors be accepted without additional consideration of more recently available information. A study may be valuable to the derivation of PALs if the study uses scientifically valid methods or provides sufficient details to determine its quality or deficiencies, contains adequate and reliable data, or provides data-driven conclusions applicable to PAL development.

Studies should be evaluated for five general principles, as described by the U.S. EPA (2003, 2012b): When evaluating the quality and relevance of scientific and technical information, Agency considerations may be characterized by five general assessment factors:

- **Soundness** - The extent to which the scientific and technical procedures, measures, methods, or models employed to generate the information are reasonable for, and consistent with, the intended application.
- **Applicability and Utility** - The extent to which the information is relevant for the Agency's intended use.
- **Clarity and Completeness** - The degree of clarity and completeness with which the data, assumptions, methods, quality assurance, sponsoring organizations, and analyses employed to generate the information are documented.
- **Uncertainty and Variability** - The extent to which the variability and uncertainty (quantitative and qualitative) in the information or in the procedures, measures, methods, or models are evaluated and characterized.
- **Evaluation and Review** - The extent of independent verification, validation, and peer review of the procedures, measures, methods, or models.

The list of guidelines for study evaluation should be established on science-based methodologies, but not be so restrictive that it removes professional judgment. Some bioassay guidelines provide a basis for selection of a robust list of study elements that, in concert with professional experience and scientific judgment, are used to qualify the data that support the development of PALs. For example, the NRC (1993), the Organization for Economic Co-operation and Development's OECD Guidelines for Testing of Chemicals (OECD, 2017), and EPA Health Effects Testing Guidelines found in the Code of Federal Regulations (40 CFR 798) provide a basis for selection.

Evaluation of specific reports and pertinent data is critical. Similar to the process for acceptance of manuscripts in peer-reviewed journals, references of interest to PAL development are subjected to critical review and analysis. The following elements for evaluating reports (adapted from NRC, 2001) provide guidance and are not intended to be prescriptive.

1. **Route of exposure.**
    a. Inhalation routes are preferred for inhalation PALs.
    b. Preference is given to oral dosing studies in which the test article is dispersed in the drinking water in developing oral PALs. . . Experiments utilizing gavage or dietary administration will also be considered. When available, studies using water as the vehicle are preferred.
    c. Intravenous administration represents a worst-case scenario for bioavailability as it assumes 100% absorption. For some chemicals, especially therapeutic agents, findings from intravenous administration may be the most robust datasets available. Inclusion and/or reliance on results from i.v. studies should be justified on a case-by-case basis.
2. **Exposure inhalation concentration or oral dose.** Factors to be considered will include, but not be limited to, nominal vs. target vs. analytical concentration vs. average concentration, degradation of the test article, exposure/dose range and intervals, the critical effect associated with the exposure/dose range being studied, etc.
3. **Dosing or exposure duration.** The experimental dosing or exposure regimen (e.g., # doses/day or # hr/day and # day/week) should be provided. Professional judgment will be used to assess relevance of the dosing or exposure duration to development of a specific PAL. Attention will be given to factors such as mode of action, latency, reversibility of effects, and metabolism. Dosing or exposure durations closely bounding the PAL-specific duration will be preferentially examined; e.g., a 2-week or 4-week experimental dosing or exposure duration would be considered more appropriate for Short-Term PAL development than would a study having a 48-hour or 10-week dosing or exposure duration.
4. **Analytical methods.** The procedures used to determine chamber concentration for inhalation exposures should be specified or described. For oral dosing, dose may be determined from the amount of test chemical placed into the vehicle (preferably drinking water).
5. **Number of subjects.** For acute studies, 5-10 rodents/sex/test group is generally acceptable, but as few as 2-3 primates or dogs/test group may be acceptable depending upon the severity of the effects observed, variability within test groups, and by the amount of change or intensity of the effect that is considered to be of biological significance. Smaller group sizes may be acceptable if the number of treatment groups is increased sufficiently. For subchronic and chronic studies, test groups should contain ten or more animals of two different species (possibly fewer for primates).
6. **Species studied.** Humans are most relevant. Historically used experimental species

including rats, mice, rabbits, guinea pigs, ferrets, dogs, or nonhuman primates are acceptable as surrogates for humans. Other species require evaluation on a case-by-case basis. It is important that the species used have an historical control history and exhibit a toxic effect that can be established as relevant to humans. The PALs assessment protocol will be consistent with human research as described in U.S. EPA (2006a).

7. **Control groups.** There should be a concurrent control group that is treated identically except for dosing or exposure to the test article and/or vehicle for the test article**.**
8. **Inhalation concentration or oral dose range.** Regimens should be selected to allow for a clear dose-response or concentration-response relationship.
9. **Observation period.** Duration of the observation period is variable based upon the onset of the effect and whether or not there is prior knowledge regarding the nature of the effect expected or the continuum of the toxic response. For rapidly occurring effects (i.e., minutes to several hours) with rapid recovery, observation periods of 3-4 days are often sufficient. For latent and persistent effects (i.e., days to weeks or longer), a minimum observation period of 14 days is recommended. For some effects, such as pulmonary damage, assessment at months following the initial effect may be necessary.
10. **Signs of toxicity.** The nature and frequency thereof should be noted during and after dosing or exposure. Relationship of effects to gender and concentration/dose should be recorded.
11. Animal studies should provide body and, where appropriate, organ weights for critical time points in the study.
12. For an ideal repeated inhalation or oral study, a NOAEL for the endpoint of concern should be established. Data pertaining to biomarkers of dosing or exposure or pre-dosing or exposure baseline values (e.g., cholinesterase activity levels) may also be important.
13. At least 3 dose levels or exposure concentrations should be used to establish a dose-response or concentration-response relationship.
14. Identifying both a NOAEL and LOAEL for observed effects level strengthens the confidence in the study.
15. Record of time of death if it occurred and note any significant/consistent latency periods.
16. For animal studies, necropsy should be conducted with at least gross effects noted.
17. Histopathological changes, clinical chemistry, and hematology data are very useful and may allow reduction of uncertainty factor(s).
18. **Stop-exposure studies**. Use of a recovery group is useful for determining the timing and degree of reversibility.
19. **Statistical analysis.** Appropriate statistical analysis of data including levels of significance is required.

4.3 Human data

The use of human data in the development of a dosing or exposure POD for health risk assessment avoids the uncertainties inherent in the extrapolation of animal data to the human response. Additionally, human data sets may provide insight into individual variability and sensitivity in the toxic response to chemical exposures based on the normal distribution of effects. These data may come from epidemiological and occupational dosing or exposure studies, case reports, or controlled clinical testing. Conversely, human data sets (especially case reports and retrospective studies) are often limited by poorly characterized or the lack of data on dosing or exposure. When human data are considered for use in the development of PALs, it is imperative that special consideration be given to assure that studies involving intentional dosing or exposure were conducted ethically with the informed consent of the participants. For

early reports, which may lack details regarding participation of human subjects, there must be assurance that such studies were conducted in accordance with guidelines for ethical standards (appropriate at the time) and with clinical supervision in place. These ethical standards may include: Nuremberg Code (1947), U.S. Army Regulation 70-25 (1962; 1990), Declaration of Helsinki (1964 and amendments up to 2000), National Research Act (1974), Belmont Report (1979), the "Common Rule," Protection of Human Subjects, (40 CFR 26, 2000), and U.S. EPA Final Rule (2006a).

5 Derivation of PAL Values

Optimally, PAL values are developed based on reports describing the dose or concentration dependent changes in the expression of effects that can be assigned to a specified PAL tier, in humans representing those thought to be generally susceptible to such effects, for durations of dosing or exposure that are in close agreement with the PAL duration of interest, and which demonstrate sufficient data to support an estimation of a threshold dose or exposure concentration (a POD) that demarcates the transition of the severity of effects from one level of severity (tier) to another. Because data sets such as these are seldom available, adjustments can be made to less robust yet reliable data, as guided below. This may include both quantitative adjustments of dosimetry and the application of uncertainty factors.

PAL values are derived according to the threshold method used for other risk values, including RfD, RfC, and MRL values. Here,

$$\text{PAL Value} = \text{POD (ADJ)} / (\text{UF} \times \text{MF})$$

Where, the route-specific (inhalation or oral) PAL value is the defined severity category or tier 1, 2, or 3 for the specified duration of 24-hours, 30-days, 90-days, or other; POD(ADJ) is the point of departure for the critical effect adjusted to a continuous exposure duration; UF (Uncertainty Factor) is the product of values for four Uncertainty Factors (described later); and MF is the Modifying Factor (described later).

Data analysis and the development of PAL values should focus on the identification of the route-duration- and tier-relevant critical effect and point of departure (POD), adjustments for areas of uncertainty regarding the chemical-specific toxic response, and dosimetry. The identification of a specific critical effect, especially when available data shows multiple effects for a given exposure, requires professional judgment. Unique, chemical-specific issues should be addressed in the PALs documentation, as required.

If data to derive a scientifically defensible PAL value are unavailable, the designation NR (Not Recommended) will be applied with a specific note on this status. In cases where data are available to enable the computation of a PAL value but the resulting value is relationally inconsistent with other PAL values (e.g., a PAL1 being very close to or higher than a PAL2 value; a 30-day PAL-1 value is lower than a corresponding 90-day PAL-1 value), or where properties of the chemical make it inadvisable to recommend a value (e.g., notable effects would be experienced in the absence of detection of the chemical), an explanation will be given with the NR designation.

Intravenous administration represents a worst-case scenario for bioavailability as it assumes 100% absorption. For some chemicals, especially therapeutic agents, findings from intravenous administration may be the most robust datasets available. Findings from the i.v. route may be

used when necessary. In these cases, procedures to adjusted i.v. doses to oral or inhalation equivalents must be clearly presented. When conducted, adjustments based on pharmacokinetic data or models should include a rationale for selection of the dose metric upon which the route extrapolation was based (U.S. EPA, 2014).

5.1 Evaluation of effects

Because the application of PALs methodology results in the development of dosing or exposure values corresponding to defined levels of severity, and because empirical observations of toxicity information are typically used as the basis for the development of these values, the identification of effects corresponding to the three established categories of severity (which may generally be characterized as producing mild, reversible effects that are not necessarily adverse; producing more severe or irreversible or escape-impairing effects; or lethality) is an important activity. NRC (1993) acknowledged this requirement relative to distinguishing CEEL-1 effects from CEEL-2 effects, "Two other grades of severity – disability and discomfort – though less well defined, place distinct demands on emergency and health care services." Given the continuum of biological responses following dosing or exposure, and the extent to which Tier effects (lethality) may be relatively easily determined, a higher level of attention toward the distinction between Tier 1 and Tier 2 effects may be expected.

The assignment of "adverse" or "not adverse" as descriptors for changes in the biochemistry or the physiology of an organism following chemical dosing or exposure, and the determination that an effect may or may not be reversible upon cessation of exposure, may be complicated. However, decisions regarding the adverse and reversible nature of chemical effects have direct relevance to selection of critical effects for derivation of PAL-1 and PAL-2 values. The selection of adverse effects may best be accomplished on a chemical-by-chemical basis, or even on the basis of an assessment under development. The National Academy of Science evaluated and described the development of toxic (adverse) responses in the context of the Toxicity Pathway paradigm (NRC, 2007). In this paradigm, chemical dosing or exposure may initially or at low doses or concentrations result in biologic perturbations, the consequences of which are related to the dose or exposure, timing, and duration of exposure. For example, adaptive changes may enable a maintenance of homeostasis, but the maintenance of homeostasis may be overwhelmed by doses or exposures of longer duration at higher doses or concentrations, resulting in the development of additional changes that may represent an adverse condition. In other cases, an observed and measurable change in a biological system may be a biomarker of dosing or exposure, which is different from a biomarker of an effect. The relative importance of such changes may also be better estimated when interpreted in the context of the Adverse Outcome Pathway (Villenueve et al., 2014). The characterization of a suite of observed and interlinked changes sufficient to constitute a Mode of Action (Sonich-Mullin et al., 2001), and to determine its relevance to the humans (Boobis et al., 2006, 2008) may be available. If so, this information can be used to increase the level of confidence in extrapolating dose or concentration response findings from experimental animals to humans.

Two recent publications from the pathology community of experts shed additional light on the adverse and reversible nature of chemical effects. Kerlin et al. (2016) recommend that a distinction between "markers of toxicity" and toxic/adverse effects should be made, with "markers of toxicity" observed in one tissue being considered more representative of an adverse condition when they are observed in conjunction with related changes in target organs, tissues, or functions. Palazzi et al. (2016) provide additional insight that cautions against binary interpretations of individual effects as representing adversity or not, and advocate for development of a complete understanding of the lesion or effect including control incidence, severity, and correlations with

other relevant effects. Holsapple and Wallace (2008) reached a similar conclusion regarding isolated findings, and recommended that changes may not represent an adverse condition when they are of a magnitude insufficient to result in a functional change. This line of thought seems consistent with the decision by the AEGL Committee to select a 22% methemoglobin concentration in humans as an endpoint consistent with a tier 1 effect (NRC, 2001) – representing an "asymptomatic or nonsensory effect" not rising to the level of a "serious or irreversible health effect."

The categorization of effects according to severity should be based on the expected health impact at the level of the intact animal or human, recognizing that the distinction between tier 1 and tier 2 effects may at times be challenging. Because of the chemical-specific nature of toxicity, it may be difficult to establish default categorizations for effects that may be generally similar among chemicals. While some information may be gained by considering effect categorizations in other risk systems (e.g., AEGLs), consideration must also be given to factors such as differences in exposure duration and differences in the availability of additional or supporting information since the previous categorization effort. Regarding categorization of health effects by tiers, several questions can be formulated. Data for the chemical, route and duration of interest can provide informative answers to questions like these.

- Is the effect morbidity or lethality? If so, it is appropriate for tier 3 consideration.
- Does the effect indicate a decrement of motor, sensory or central nervous system function? If so, whether reversible or not, it may indicate a decreased ability to escape a contaminated environment and is appropriate for tier 2 consideration.
- Does the effect represent a non-life threatening decrement of function of organs, tissues or physiologic or biochemical processes? If so, the extent to which is represents a serious condition or a reversible condition can contribute to its characterization as tier 1 or tier 2 effect.
- Does the effect represent a non-life threatening alteration of tissue organization or structure (e.g., histologic changes)? If the changes are not expected to produce a serious decrement of function (e.g., gas exchange in the alveolus), and may be expected to be reversible or repairable upon cessation of exposure, they may be classified as tier 1 effects. If the changes are expected to produce a serious decrement of function, regardless of the expectation of reversibility, they may be classified as tier 2 effects.
- Does the effect represent a mild effect, not seriously impacting function, not expected to reduce the ability to escape a contaminated environment, and for which a return to normal function is expected upon cessation of exposure? If so, the effect may be categorized as a tier 1 effect.
- Does the effect represent an adaptive change in a baseline value for a physiologic or biochemical parameter (which is not expected to represent a more serious effect)? If so, it may be appropriate to classify the response as a tier 1 effect.

5.1.1 Mechanistic considerations

For some chemicals, mechanistic data may inform the selection of the most appropriate approach to duration extrapolation. This concept has been operationalized by ten Berge and others, where responses from a series of concentrations exposed for a series of durations have been compared. It can sometimes be seen that the same cumulative exposure (concentration × time; e.g., expressed in units of ppm-minutes) do not produce consistent responses. Likewise, some studies have demonstrated that animals exposed to the same daily dose (more or less, continuously) via drinking water or by a single bolus gavage do not develop the same types or severity or response. Compressing the cumulative daily dose into a shorter exposure period or into a bolus dose can

alter the toxicokinetics of the compound relative to multiple individual exposures to lower (fractional) doses encountered over longer time periods. Different toxicokinetic patterns may include higher maximal concentrations in blood and tissues following short-duration exposures or bolus doses, and consideration should be given to the possibility of metabolic saturation. Whether compressing the daily dose into shorter periods increases or decreases toxicity will vary among chemicals, and with respect to whether the potentially saturated metabolic process(es) represents a bioactivation or a detoxication process, among other things.

Some toxicities are based on mechanisms that are relatively slow to develop. Particularly true for the shortest PALs duration (up to 24 hours), lethality may not become evident until hours or days following the end of the 24-hour period since initiation of the exposure. For these reasons, it is important to carefully evaluate reports that include observations made following a post-exposure (recovery) period, during which latent effects may become manifest. This may be particularly for the evaluation of effects at short exposure durations for chemicals which are poorly metabolized and slowly cleared from the body.

The lack of a mechanistic understanding induces significant uncertainty in the adjustment of doses identified on the basis of longer-term exposure durations for shorter exposure durations on the basis of a mathematical adjustment based on (e.g.) the number of days exposed.

5.2 Identification of critical effect

PALs directly address the progression of severity of toxicity with increasing dose or exposure as the basis for deriving multiple health-based levels of exposure. None of these tiers of severity may be directly comparable with the severity (or lack thereof) of effects or levels used as the basis for risk values intended for broad population applicability, for continuous dosing or exposure over a lifetime (e.g., chronic IRIS Reference Dose or Reference Concentration values). The evaluation of chemical-dependent effects requires considerable judgment regarding the nature, severity, and permanence of their expression. Dose- or concentration-response data for the critical effect is used to determine the point of departure (POD), which serves as the quantitative basis for PAL value derivation. The key study is that manuscript or report that describes the dose- or concentration-response data for the critical effect, and identifies the POD. The selection or identification of the critical effect and its POD also identifies the key study.

The critical effect is a response that is consistent with the PAL tier levels and is characterized in the key study (and supporting studies where relevant). The POD for the critical effect serves as the basis for deriving a specific PAL value. It is imperative that the critical effect be of a severity consistent with the PAL tier. Selection of effects or POD for effects of notably lesser severity than the specific PAL tier may result in unrealistically low PAL values and inappropriate emergency response (e.g., unnecessary evacuation or delayed reentry). When circumstances require reliance on an effect of higher severity (i.e., when data fail to identify an effect of the appropriate severity), the POD for the more severe effect will require adjustment via the application of an uncertainty factor (described below).

Characterization of the critical effect should include:

- Species in which it occurred
- Gender and strain if relevant
- Exposure or dose duration associated with the effect
- Dose- or concentration-response information including an estimate of the threshold for the effect
- Evaluation of the strength of the association between exposure or dose and effect,

including consideration of the quality of the data
- Detailed description of the effect including the actual physiological/toxicological response
- Target organ or tissue, if data warrant
- Clinical chemistry
- Gross pathological and histopathological correlates, if these are available
- Post-exposure observation period, if applicable
- Data quality issues

5.2.1 Severity of Effects

The evaluation and characterization of effects to serve as the basis for PAL value development is based on several precedents established by accredited risk assessment bodies deriving values for emergency response purposes. The NRC provided guidance for evaluating data and selecting health effects for application in setting exposure levels for three levels of severity, for one-hour Community Emergency Exposure Levels (CEELs) for Hazardous Substances (NRC, 1993):

- Exposures below CEEL 1 values are unlikely to lead to discomfort
- Exposures above CEEL 1 values result in an increasing likelihood of discomfort, but for which the direct toxic effects of the chemical are unlikely to lead to disability
- Exposures above CEEL 2 values result in an increased likelihood of disability (disability becomes increasingly common), but for which the occurrence of death or life-threatening effects are unlikely
- Exposures above CEEL 3 values result in an increasing likelihood of the occurrence of death or life-threatening effects

This three-tiered system of exposure values and its characterization of tier-relevant types of effects was also implemented in guidance that was used to develop Acute Emergency Guideline Levels (AEGLs) by the NRC (2001) which include durations of exposure from ten minutes to 8 hours, and has been used as the basis for characterization of effects for development of PAL values.

5.2.1.1 PAL-1

PAL1 represents a threshold no-effect-level (PAL-1 effects need not necessarily be “adverse”) immediately above which there may be reversible, measurable changes from baseline values of various biomarkers of dosing or exposure, or subclinical changes in physiologic responses. The critical effects upon which PAL-1 may be based include biomarkers such as normal compensatory changes in clinical chemistry values (e.g., threshold for increased activity of enzymes associated with normal metabolism and detoxification pathways, threshold methemoglobin formation, or red blood cell cholinesterase activity inhibition) or thresholds for reversible physiological responses (e.g., slight miosis or lacrimation, slight nasal irritation, or odor or taste detection). Careful consideration must be given, however, to developing PAL-1 values using data for effects that may be imperceptible or innocuous but which could be considered precursors of a significant toxicological process (e.g., hemolysis), especially for chemicals for which the dose- or exposure-response curve is extremely steep (e.g., arsine, some metal carbonyls). In such cases, the PAL-1 must be sufficiently protective to avoid an unacceptable response at the PAL-1 level. In addition, the critical effect cannot be more appropriate for PAL-2. If reversibility following cessation of dosing or exposure is not demonstrated, some justification of the effect, at the dose level or exposure concentration and the duration encountered should be provided.

5.2.1.2 PAL-2

PAL-2 represents a threshold for effects characterized as serious, possibly irreversible, or escape-impairing. Multiple effects may be characterized as PAL-2 effects, and the suite of PAL-2 effects should be expected to vary from chemical to chemical, and they may also vary according to dosing or exposure duration for a given chemical. Professional judgment should be used to determine the severity of the effect. Examples of severe or irreversible effects possibly occurring above PAL-2 might include clinical signs of CNS depression, pulmonary damage (e.g., pulmonary edema, hemorrhage, congestion, or evidence of pathologic changes), ocular damage, gastrointestinal bleeding, organ injury, clinically relevant hemolysis, or initiation of asthmatic episodes. A response that results in an increased potential for prolonging the effects of exposure or otherwise subjecting one to a more hazardous dose or exposure would also be considered as basis for PAL-2 development.

Latency in expression of an effect (e.g., arsine and hemolysis-induced renal failure, phosgene and pulmonary edema) and the possibility of increasing severity in the effect after cessation of exposure (e.g., sulfur mustard exposure and pulmonary damage) must be considered. Although reversible, escape-impairing effects such as CNS depression, severe dizziness, vertigo, convulsions, ataxia or other motor deficiencies, and impaired vision are consistent with PAL2 severity. The evaluation of developmental, reproductive, and endocrine effects may be relevant to all durations for PAL-2 development.

5.2.1.3 PAL-3

PAL-3 values represent estimated human lethality thresholds. At exposures equivalent to the PAL-3, serious toxicity is to be expected. Because PAL-3 levels generally will be developed based upon lethality data in animals, PAL development must consider the uncertainties inherent in such animal-to-human extrapolations while not arbitrarily or excessively reducing PAL-3 values. Relevant experimental findings include early death, morbidity, and the rapid onset of life-threatening toxicities. The inclusion of a post-exposure observation period will increase confidence that the results do not over-estimate a threshold for lethality for the experimental dosing or exposure duration. When available, interim observations (e.g., the time of death) can also provide important quantitative details. For example, the authors of a 90-day dosing or exposure study may only describe lethality indirectly by reporting survival to study termination, or in the form of survival data which may (inadvertently) quantify lethality at only after (e.g.) 1 or 30 days.

5.3 Identification of the Point of Departure (POD)

The POD is the actual dose or exposure concentration and duration associated with a critical effect used quantitatively as the basis for derivation of the respective PAL. This exposure or dose serves as the basis for quantifying PAL values. For the inhalation exposure route, the concentration used for operational derivation of the PAL will be expressed as ppm or mg/m^3 and exposure duration. For oral dosing, the dose will be expressed as mg/kg/d. Ideally, the POD comes from human exposure data or a well-conducted animal study in a species whose anatomy, biochemistry and physiology is representative of the human. When the expression of the oral dose in terms of mg/kg-d requires translation from values reported in original reports (e.g., ppm in diet or mg/L in drinking water), conversions should be clearly presented and to the extent possible include references to previously reviewed or otherwise reliable standards, methods, or parameter values.

NRC (1993) indicates that the derivation of a CEEL value may be based on a POD identified as a NOAEL or a LOAEL, "An additional 10-fold UF may be introduced when deriving a CEEL-1 from a LOAEL instead of a NOAEL, or a CEEL-2 or CEEL-3 from appropriate LOAELs or FELs." (FELs are frank effect levels, that is, levels that can cause incapacitation or death.) The concept of "threshold" pertinent to animal POD values is given some attention in the context of uncertainty factor development by NRC (1993): "For agents that are considered to produce threshold effects, select an appropriate uncertainty factor of 1 or greater for endpoints affording NOELs, NOAELs, LOELs, or thresholds." (NOEL is no observed effect level; LOEL is lowest observed effect level.) This description of thresholds seems to indicate that a POD value may be based on non-traditional POD effects.

5.3.1 The Threshold Concept

In presenting the approach to noncarcinogenic effects, NRC (1993) indicates, "The existence of a so-called threshold dose or concentration is supported by but not limited to the fact that the toxicity of many agents is manifest only after the depletion of a known physiological reserve." The threshold concept is also central in most contemporary noncancer risk value systems. However, in the establishment of CEELs methodology (NRC, 1993), it was also recognized that the resulting risk levels are not themselves bright lines, specifically: "CEELs should indicate exposures that would be thresholds for the occurrence of (1) death or life-threatening effects, (2) disability, or (3) discomfort in the population. At such a threshold concentration [a CEEL value], a small proportion of the population might exhibit effects." This was based on considerations of the imprecision relating to demarcation of risk categories, the imprecise nature of underlying toxicity data as might be derived in various sources, and because the incidence of effects at a given CEEL level will depend on the proportion of hypersusceptible people in the population. NRC (1993) reiterates, "[T]he intent of CEELs is not to provide absolute assurance that everyone at risk will be protected under all circumstances, and thus the uncertainty factors should be chosen with the understanding that hypersusceptible persons might not be protected."

Discussions regarding the establishment of AEGL values through the identification of tier-specific endpoints and PODs (NRC, 2001) references previous CEELs guidance (NRC, 1993), pages 10, 12, and 21 for clarity and consistency. In these discussions, NRC (2001) reiterated points regarding the selection of critical effects and PODs. In framing the AEGL values, NRC (2001) indicated that,

> "Because the data and methodologies used to derive AEGLs or any other short-term exposure limits are not sufficiently precise to make a distinction between a ceiling value [the highest no effect level] and a threshold value, no distinction has been made with respect to AEGL values. No fine line can be drawn to precisely differentiate between a ceiling level, which represents the highest exposure concentration for which an effect is unlikely to occur, and a threshold level, which represents the lowest exposure concentration for the likelihood of onset of a given set of effects. Hence, AEGLs are not true effect levels. Rather, they are considered threshold levels that represent an estimated point of transition and reflect the best efforts to establish quantitatively a demarcation between one defined set of symptoms or adverse effects and another defined set of symptoms or adverse effects. Therefore, in the development of AEGLs, the NAC/AEGL Committee selects the highest exposure level from animal or human data where the effects used to define a given AEGL tier are not observed."

Frequently, the POD will not be precisely defined in the available study reports. Depending on the PAL level being derived, this will necessitate estimation of a threshold for the effect or, for

some PAL tiers, a minimal or no effect level. For a threshold estimation, this usually entails selection of the ceiling, i.e., the highest dose or exposure that does not cause a relevant adverse effect (a NOEL, a NOAEL) for the specific PAL tier. For an actual effect level (a LOEL, a LOAEL), the POD generally will be the lowest reliable exposure or dose causing a minimal relevant effect consistent with the PAL tier definition.

5.3.1.1 Benchmark Dose Modeling (BMD)

Benchmark dose modeling has seen application in many risk assessments including those based on dichotomous and continuous data, and its application to dose response modeling should be considered during PALs development. The traditional approach to determining the point of departure based on NOAEL or LOAEL values has disadvantages including, (1) it is limited to the doses tested, (2) response levels may not be comparable, standardized or identified, (3) the response level at a NOAEL is not determined, (4) responses at other tested doses are not considered, (5) a NOAEL is not always available, and (6) statistical comparisons are impacted by sample size. The application of benchmark dose modeling imparts a greater level of confidence to a derived POD (a BMD or BMDL) value for several reasons including consideration of the entire range of observations across all doses and not restricting the definition of the POD to one of the studied doses. More specifically, BMD modeling (1) does not identify a point of departure that is limited to one of the doses tested, (2) removes the impact of dose spacing on the identification of the point of departure, (3) takes responses at all doses into account, (4) allows for flexibility in determining the level of biological relevance in the effect, (5) provides for an increased level of consistency in the comparison of endpoints across chemicals and studies, (6) allows for the integration of data from comparable studies in quantitative analysis, and (7) is performed using standardized software and supported by peer reviewed documentation.

However, its application can also be resource-intensive. While not presuming the intentions of the NAC/AEGL Committee, some consideration of BMD modeling across all three AEGL tiers may have resulted in their indication that, "these methods will generally be considered for an acute lethal endpoint. Their use to set AEGL-1 and AEGL-2 values will be considered on a chemical-by-chemical basis." Young et al. (2009) described the approach used by Oak Ridge's Expert Consultation Panel which seems to indicate more broad reliance on BMD modeling across tiers: "When data are sufficient, the Benchmark Dose (BMD) or benchmark concentration (BMC) for inhalation exposure terms (U.S. EPA, 1995, 2007 [2015]) should be used to derive an estimate (95% lower confidence limit) of the exposure expected to cause a specified response incidence. The benchmark is usually a 1% to 5% response incidence. For PAL derivation, a BMD_{01} (BMC_{01}), or the lower limit of the BMD_{05} or BMC_{05} ($BMDL_{05}$ or $BMCL_{05}$), *for a specific biological effect* [italics added] may be considered."

Because of the Provisional and Advisory nature of PAL values, because of the recognized variability based on the normal distribution within the study population, the sometimes imprecise nature of the characterization of biological effects, and because of the intent of PAL values to provide information generally describing the increase in biological severity of effects with respect to dose or concentration, requirements (recommendations, suggestions) for broad application of BMD modeling for all types and severities of effects should be carefully considered. The application of BMD modeling to estimate the threshold and identify the point of departure for PAL-3 effects (e.g., lethality) should be undertaken when the data permit, BMD modeling may also be used to estimate the threshold (point of departure) for PAL-1 and PAL-2 effects when it is determined that the uncertainty in the threshold (point of departure) estimated by other means undermines confidence in the derived PAL value. Citing an analysis

of acute inhalation lethality data by Fowles et al. (1999) in which BMC lower confidence limit values (BMC_L values) were compared to No-Observed-Adverse-Effect-Concentration (NOAEC) values, NRC (2001) seemed to indicate that (for acute lethality data) a BMR of 10% "may be too high a response rate," compared to BMR values of 5% or 1% (more fully described in Section 5.3.4). NOAEC is the no observed adverse effect dose or concentration. In all BMD applications, the benchmark response value (e.g., 1%, 5%, 10% response rate) should be determined on a case-by-case basis.

5.3.2 PAL-1 Point of Departure

The threshold concept has been specifically clarified with respect to tier-1 effects relative to AEGL values: "Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and non-disabling odor, taste, or sensory irritation, or certain asymptomatic, non-sensory effects" (NRC, 2001). NRC (2001) also clarified the selection of a POD value, indicating, "The highest concentration not producing an AEGL-1 endpoint or effect levels for mild sensory irritation, asymptomatic, or non-sensory effects, such as methemoglobin formation (22%) or altered pulmonary function (transient changes in clinically insignificant pulmonary functions of a hypersusceptible individual), have been used as AEGL-1 endpoints." It can thus be inferred that AEGL values were established with the expectation that such an exposure might result in an increase in a parameter such as methemoglobin concentration of up to 22% or a decrease in FEV1 of up to 20%.

Tier 1 values, as established for AEGL-1 values do not represent no-effect exposure conditions, as acknowledged by NRC (2001; 1993). Below AEGL-1 values "there may be specific effects, such as the perception of a disagreeable odor, taste or other sensations (mild sensory irritation)," which NRC explains by stating, "Since there is a continuum of discomfort in which it is difficult to judge the appearance of "discomfort" in animal studies and human experiences, the NAC/AEGL Committee has used its best judgment on a case-by-case basis to arrive at appropriate and reasonable AEGL-1 values."

There is a broad range of measurable changes in biological systems (changes in biomarkers, adaptive changes, adverse but reversible changes, etc.) that may be observed below exposures that produce more severe possibly irreversible changes or changes that may impair an ability to escape a contaminated environment (tier 2 effects). The POD chosen for PAL-1 derivations may represent a no-effect level (dose/exposure) for the critical effect (e.g., mild irritation), but is an exposure or dose that may be expected to produce measurable changes in some parameters not chosen as the critical effect (e.g., 5% inhibition of plasma acetylcholinesterase activity).

5.3.3 PAL-2 Point of Departure

The NAC/AEGL Committee addressed two possibilities for establishing the threshold and the point of departure for Tier 2 effects. On the basis of acceptable data describing a tier 2 effect, the NAC/AEGL Committee indicated a preference for determining the POD value by "estimate[ing] a NOAEL for serious or irreversible effects or effects that impair escape" to develop AEGL-2 values (NRC, 2001). If data describing the development of tier 2 effects are lacking, then the highest exposure that caused tier 1 effect but did not cause a tier 2 effect may be selected as the POD. If so, this value may be subjected to a severity adjustment (see section 5.4.4). Section 5.8 presents an alternate method to estimate a PAL-2 value on the basis of a derived PAL-3 value.

5.3.4 PAL-3 Point of Departure

Lethality may not become evident during the course of dosing or exposure. Optimal confidence can be placed in estimates of the threshold for lethality when studies include a post-exposure observation period. Several approaches to determine or estimate the threshold for lethality from the results of studies in which lethality is observed (as suggested by NRC, 2001) may be employed. These include: (1) identify the lethality threshold as the highest dose or concentration that does not produce lethality, (2) estimating a lethality threshold as one-third of the animal LC_{50} (concentration lethal to 50% of the exposed group) or LD_{50} (dose lethal to 50% of the dosed group), or (3) calculating a lethality benchmark response (e.g., 1% or 5% response level) by the BMD method (U.S. EPA, 1995, 2012c, 2015) or other methods such as Litchfield and Wilcoxon (1949).

Estimation of a lethality threshold as one-third of the LC_{50} or LD_{50} may be considered when data are insufficient for a benchmark calculation. This approach has been used in the AEGL Program (NRC, 2001) as based on inhalation exposures by analyses conducted by Fowles et al. (1999). The approach has been subsequently evaluated and endorsed for application to acute lethality data from inhalation exposure by Rusch et al. (2009). Fowles et al. (1999) analyzed 120 acute lethality data sets using BMC (benchmark concentration) methods and reported that the ratio between the LC50 and a nonlethal exposure averaged about 2, with the 90th and 95th percentiles being 2.9 and 3.5, respectively. The ratios ranged from 1.1 to 6.5. This approach is especially valid for those chemicals with a steep concentration-response relationship. Increased confidence in this approach is developed when a weight-of-evidence approach comparing the POD value for lethality (as estimated above) with dose or exposure response data for non-lethal effects derived for the same duration, and/or with lethality data for other durations. For some chemicals, estimation of a tier 3 value may necessitate other, even less quantitatively robust options. In the absence of a statistically determined LC50 or LD50, data from a well-designed and conducted study describing the dose or exposure dependent frequency for lethality (e.g., doses or exposures producing 25%, 60%, and 80% lethality) may be used as either the basis for a one-third reduction, or as the basis to estimate a 50% response rate upon which to derive a one-third reduction. The one-third reduction is more conservative than using the highest non-lethal concentration. (Rusch et al. 2009) It is recommended that such analyses be supported by other data indicating that the estimated value is a plausible estimate of the lethality threshold as described above and in Section 5.8.

In cases where data are insufficient for a quantitative estimate (e.g., a benchmark calculation or a no-effect level) of a human lethality threshold, the PAL-3 may be derived by analysis of the best available data. This analysis should attempt to estimate the highest exposure/dose that will not result in human lethality. Data descriptions should include the species, exposure concentration or dose level, and the associated effects, and how the data relate to the lethal response (e.g., is the effect part of the continuum of toxicity that would lead to a lethal response). Because this approach may lack in-depth quantitative analysis, all assumptions and rationales should be thoroughly described.

Calculation of a benchmark lethality threshold provides a more accurate and defensible POD (see section 5.3.1.1.) for PAL-3 values but requires sufficient dose- or exposure-response data (data requirements for these methods are provided in U.S. EPA, 1995; 2007). Regardless of the specific method used, estimated lethality thresholds should always be compared to available toxicity data to assure some level of continuity and scientific validity.

In the absence of lethality data, exposures or doses known to cause extreme toxicity may be

considered for PAL-3 development with appropriate rationales clearly stated and, where possible, supported by data from laboratory animal experiments or human doses or exposures. For example, severe morbidity, an effect frequently noted in lethality studies with laboratory animals, may be considered a critical effect appropriate for PAL3 development.

Similarly, AEGL-3 values define the highest exposure level that does not cause death or life-threatening effects. NRC (2001) specifically treated the selection of the POD in the context of a no-effect level, indicating that when data were amenable, a benchmark dose modeling analysis to identify the $BMCL_{05}$ value could be used to determine the POD. Alternately, the point of departure can be determined as "the highest experimental exposure that did not cause lethality in an experiment in which death was observed" or by a fractional reduction of the LC_{50} value. In this case, AEGL guidance indicates that a point of departure may be estimated by dividing an LC_{50} value by 3.

5.3.5 Duration Adjustment of the Point of Departure

PALs are developed for doses or exposures assumed to be continuous, for durations of (e.g.) up to 24-hours, up to 30-days, up to 90-days, or other durations as required. Experimental data used as the basis for PAL derivations are often developed using a *discontinuous* or intermittent experimental dosing or exposure protocol (e.g., 6 hours per day, 5 days per week for 4 weeks). This dosing or exposure pattern differs from the PAL-specific durations (e.g., an exposure assumed to be *continuous* for the PAL duration), requiring a duration adjustment to account for differences in discontinuous (experimental, observational) versus continuous (human, anticipated) exposures. This section addresses adjustments for intermittent dosing or exposure (e.g., inhalation exposures conducted for 6 hours per day, 5 days per week; oral exposures via dosing 5 days per week).

Because of their technical nature, inhalation toxicity studies often include a daily exposure for a number of hours less than a typical work day (often 6 hours per day), and exposures for often 5 days per week. This requires an initial duration extrapolation to the 24-hour period, as discussed in section 5.3.5.1. Whether time-normalizing short exposure periods to the 24-hour period via Haber's Law or the ten Berge approach, consideration should be given to mechanistic data. These data may indicate that the effects observed from shorter (e.g. 6 hours) periods of exposure to higher concentrations may not be similar to the effects observed from longer (e.g., 24 hours) periods of exposures to proportionately lower concentrations. Reasons may include the saturation of metabolic processes by higher concentrations, not observed at lower concentrations, the inhibition of repair processes by higher concentrations, etc.

By convention, oral doses are typically expressed in units of mg/kg per day. Oral studies in animals often involve dosing via drinking water or feed, representing an exposure scenario consistent with expectations for human exposure conditions. Alternately, animals may be exposed via oral gavage (neat or in an aqueous or organic vehicle). Exposure via feed or drinking water allows the exposure to be temporally dispersed over the day, while gavage dosing (often selected on the basis of experimental convenience or cost) includes a bolus administration, concentrating the daily dose into a single unit of administration. This difference in dosing produces differences in the pattern of internal (tissue) exposure, and can serve as the basis for differences in responses, as well. Doses administered as a bolus have a higher potential to overwhelm detoxication pathways and repair capacity, resulting in a pattern of toxicity different from that observed from drinking water or feed exposures.

Available mechanistic information should be considered (see section 5.1) when conducting a

duration extrapolation, whether from periods of less than 24 hours to 24 hours, or from periods of less than one week to one week. When the toxicity data for a chemical indicate that such an adjustment is not valid, it should not be conducted (e.g., adjusting exposures by hours per day for irritant gases producing a pulmonary effect).

When experimental exposure durations are not continuous, extrapolation from the reported time-specific exposure concentration or dose to an equivalent concentration/dose for a PAL-specific period may be required for some chemicals (e.g., those inhaled toxicants producing effects not characterized as irritation). When justified on the basis of the type of toxicity demonstrated, the first step of the duration extrapolation involves duration adjustment to the day (the 24-hour period of dosing or exposure), and this is done differently for oral and inhalation studies. The second step adjusts the number of days per week the animals are dosed or exposed adjust the dosing or exposure to 7 days per week.

5.3.5.1 Inhalation Data

Inhalation points of departure are typically expressed in units of concentration and time (e.g., 5 mg/m^3 for 4 hours, 5 days per week). Because PAL values are applicable to continuous human exposures, intermittent experimental exposure data require adjustment into equivalent measures of continuous exposure. The RfC methodologies require the use of an exposure value adjusted (ADJ) for continuous exposure ($NOAEL_{ADJ}$ or $LOAEL_{ADJ}$). Because the PAL tiers are based on threshold effect levels, POD_{ADJ} is a more appropriate term. For example, an experimental exposure of 5 mg/m^3 identified as the exposure concentration associated with the critical effect in a study utilizing a 4 hrs/day, 5 days/week protocol may be adjusted to continuous exposure by:

$$POD_{ADJ} = 5\ mg/m^3 \times [(4\ hrs/day)/(24\ hrs/day)] \times [(5\ days/week)/(7\ days/week)] = 0.59\ mg/m^3$$

The two-part inhalation duration extrapolation procedure first accounts for intermittent exposure with respect to hours per day, then with respect to days per week (when applicable). However, many chemicals exhibit an exponential relationship between exposure duration and effect ($C^n \times t = k$). For acute exposures (durations < 24-hr), an attempt should be made to empirically derive a time scaling factor (i.e., the exponent 'n') if data are available. For mild irritation effects, it is recommended that no extrapolation from the experimental exposure duration be performed. If there is reason to believe that continued exposure may potentially result in greater pulmonary damage (e.g., increased edema), extrapolation may be appropriate.

Haber's Law traditionally has been used to relate exposure concentration and duration to a toxic effect (Rinehart and Hatch, 1964), but may apply to a small and sometimes undefined range of exposure concentrations. Specifically, the equation implies that exposure concentration or duration may be adjusted to attain a cumulative exposure constant (*k*) which relates to a toxic response of specific magnitude. Work by ten Berge et al. (1986) affirmed that chemical-specific relationships between exposure concentration and exposure time may be exponential rather than linear; i.e., the expression now becomes $C^n \times t = k$, where n represents a chemical-specific exponent. Upon examining the concentration and time relationship of the lethal response to approximately 20 chemicals, ten Berge et al. (1986) reported that the empirically derived value of n varied from 0.8 to 3.5. The n values for some of these values are presented in NRC (2001, page 95). The value of the exponent (n) is determined by the relationship between exposure concentration, exposure duration, and cumulative response, such that if n = 1, the toxic response to the chemical is dependent solely upon the product of concentration times time. (i.e., a linear

relationship, or Haber's Law where concentration and duration are equally important). Generally, values for $n < 1$ result when the exposure duration is the primary determinant of the cumulative response and values for $n > 1$ result when the exposure concentration is the primary determinant of the cumulative response.

Although ten Berge et al. (1986) considered only lethality data, where adequate data are available (i.e., multiple exposure concentration-exposure duration combinations all of which produce a quantitatively similar response), a chemical-specific exponent (n) for use in extrapolating available exposure data to specific durations may be calculated for nonlethal end-points; confidence in this approach is increased when it can be demonstrated (or reasonably assumed) that progression of the non-lethal effects to lethality is likely. The time scaling exponent (n) for a given study and PAL duration is derived by linear regression of the log-transformed exposure concentrations and exposure time data. Although debate continues regarding the placement of the exponent in the expression $C^n \times t = k$, PALs will be derived using the exponent for the concentration variable.

The linear regression is of the form

$$Y = a + bX$$

where Y = predicted dependent variable and X is the independent variable, a is the y intercept, and b is the X intercept. The log transformation of $C^n \times t = k$ becomes

$$\log C = (\log k)/n + (-1/n) \times \log t$$

where C is the predicted exposure concentration for a given exposure duration, t. The expression $(\log k)/n$ is the Y intercept of log C vs. log T plot, and $-1/n$ is the slope of this plot.

It is important to emphasize that the response associated with the cumulative exposure constant (k) must be a response that can be definitively quantified. The data must be discontinuous quantal data (e.g., live/dead such as LC_{50} or LD_{50} values) or continuous data (e.g., serum enzyme activity in International Units) for which precise quantitation of the response is possible.

If data are unavailable for empirically deriving the exponent (n), a default value for n may be applied. In a previous analysis of concentration-time response data for numerous chemicals (NRC, 2001), values of 1 and 3 for n were identified as the upper and lower bounds of the range of exponent values. Specifically, it was recommended that for extrapolation from longer to shorter exposures, $n = 3$ would be appropriate while $n = 1$ would be applied to extrapolations from shorter to longer exposure durations.

Regardless of the exponent used, the resultant extrapolated value should be evaluated in context of other data to verify its validity. Careful attention must be given to extrapolations over extreme time intervals (e.g., extrapolating the results of a 1-hour exposure to a 24-hour duration). For these cases, analysis of relevant and appropriate data and scientific judgment are especially necessary to assess validity of the temporal extrapolation. With the logical exception of deriving 24-hour inhalation PAL values, once intermittent exposures are adjusted to the continuous daily exposure (the first step in duration adjustment), exposure concentrations are extrapolated to the week by accounting for the number of exposure days per week (as described for oral dosing, section 5.3.5.2).

5.3.5.2. Oral Data

When laboratory animal studies involve discontinuous treatment regimens (e.g., 5 days/week for gastric intubation dosing), adjustment of such discontinuous dose regimens to the targeted human exposure scenario (continuous, daily exposure) is necessary for the development of (e.g.) a 30-day oral PAL values. This involves converting the intermittent dosing (e.g., 5 days/week) to a continuous dosing (e.g., 7 days/week) according to the second step of the duration extrapolation shown for inhalation exposures (above; U.S. EPA, 1988a) and consideration of what effect the vehicle (e.g., food vs. solvent) may have on a chemical's toxicity. For example, if a point of departure dose were 100 mg/kg, administered orally 5 days per week, the duration-adjusted POD value would be derived:

$$\text{POD adj} = 100 \text{ mg/kg} \times (5 \text{ days} / 7 \text{ days}) = 71 \text{ mg/kg-day}$$

This completes the duration adjustments of the POD value. When necessary, the extrapolation of duration-adjusted point of departure values across broader ranges of time is accomplished by the application of the Time Extrapolation Uncertainty Factor for (UF_T), described in section 5.4.3.

5.4 Uncertainty and Modifying Factors

PAL values are intended to represent best estimates of dosing or exposure associated with three levels of severity. They are both provisional and advisory in nature, and their application in emergency response activities should be in conjunction with other available information. This application implies a requirement that their derivation be based on methods that are reliable. As such, a technical treatment of uncertainty and variability are typically beyond the scope of PAL values. However, these concepts should be treated at some level.

Oftentimes, the key study and the overall data set are lacking in some critical aspect (e.g., the study is not conducted for a duration directly relevant to the PAL duration under evaluation or the study does not identify a NOAEL for the chosen effect) and, therefore, development of the PAL will necessitate adjustment with uncertainty factors or modifying factors to account for extrapolations.

The extrapolation of findings from test species (even from humans) is necessary to estimate cumulative dose or exposure in the general population, encountered for longer durations than experimental durations that may produce effects of a given type or magnitude (severity). Such an extrapolation process is possible only when the necessary steps are completed; when specific data are lacking, the data gap must be filled by the application of default assumptions, hence the development of the uncertainty factors. Because these factors are multiplicative (e.g., the total uncertainty factor value is a product of the values of the individual uncertainty factors), two requirements emerge. First, all gaps require the application of an uncertainty factor, and second, uncertainty factors must have a numerical value. Even when an extrapolation step is covered by available data, the uncertainty factor for the step is included, but is given a value of 1. Uncertainty factors in PAL risk values are generally similar to uncertainty factors used in other risk systems, as explained below. PAL values include uncertainty factors for extrapolation:

1) from animals to humans (interspecies extrapolation uncertainty factor, UF_A),
2) for extrapolation to account for variation in sensitivity among humans (intraspecies extrapolation, UF_H), 3) to account differences between the duration of the experimental exposure and the duration of the PAL value being estimated (UF_T), and 4) to account for differences

between the severity of the effect chosen as the critical effect and the tier category for the PAL value being estimated (severity adjustment uncertainty factor, UF_S).

An additional factor, the Modifying Factor (MF), is used in PAL derivation and should be distinguished from the Database Uncertainty Factor, as applied in the derivation of RfD, RfC, and other risk values. This is further explained in section 5.4.5.

Application of each UF has been described in detail for derivation of both oral and inhalation reference values (i.e., chronic oral RfD and inhalation RfC values), which address noncarcinogenic effects of substances due to long-term daily exposures (Dourson and Stara, 1983; Dourson, 1994; Dourson et al., 1992; U.S. EPA, 1989b; US EPA, 1994). Application of some of the UFs has also been described for derivation of acute values designed for emergency planning (NRC, 2001). Concepts developed the for use of UFs in chronic and acute scenarios can be used as a guide to application of UFs in the derivation of PALs as discussed below for each of the defined extrapolation steps (representing potential sources of uncertainty). It is important to account for the species in which the effect is quantified, the severity of the effect, the magnitude of its expression, and the duration of dosing or exposure when deciding which UFs are relevant to the respective PAL value. In addition, the value of each UF should be specific for each chemical, route, tier, and duration. As such, these values should not be expected to be entirely consistent for the range of PAL values determined, but their respective values should be determined by consistent application of methods and the basis for their values clearly described. This is discussed in sections 5.4.1-5.4.5.

To allow for optimally reliable assessments, it is necessary to:

- Carefully analyze the uncertainties and incorporate this uncertainty into PAL development
- Derive PAL values that are scientifically defensible based upon reliable data
- Evaluate PAL values relative to the overall data/weight-of-evidence for the specific chemical

NRC (1993) cautioned against the selection and application of uncertainty factors without specific consideration of the *intent* of CEELs values, indicating, "In the case of CEEL-2, uncertainty factors must be balanced against the inherent risk associated with actions, such as evacuations, that might be taken as a result of application of CEELs. Large uncertainty factors, which might be appropriate with chronic exposure limits, such as PELs [permissible exposure limits], might be associated with increased risk to the community in the application of a CEEL-2."

5.4.1 Interspecies dosimetry adjustment uncertainty factor (UF_A)

One of the fundamental assumptions in human health risk assessment is that the human is more susceptible to the toxic effects of a chemical than the test animal species unless data can establish the relative sensitivity between the species in question. Thus, in the absence of data describing the response in humans, the default value of 10 is used for UF_A. Dosimetry corrections for animal-to-human conversion are frequently an issue of concern in the development of toxicity values and are a component of interspecies variability. Specifically, it is important to assess as accurately as possible the relationship between the exposure or dose in the experimental animal and the exposure or dose predicted to produce an equivalent effect in humans.

The subdivision of UF_A into toxicokinetic and toxicodynamic components has been accomplished (U.S. EPA, 1994; WHO, 2005), closely followed by the development of methods

to quantify interspecies differences in each component. Interspecies adjustment for non-carcinogenic effects results in an estimation of a Human Equivalent Concentration (for inhaled toxicants) and a Human Equivalent Dose (for orally encountered toxicants). Various guidelines and standards have been developed that often incorporate extensive algorithms to estimate animal-to-human inhalation exposure adjustments. Several methods have been proposed to adjust for differences in the delivery of an inhaled dose to target tissue in the respiratory system (U.S. EPA, 1994) and systemic targets (U. S. EPA, 1994; NRC, 1993), on the application of allometric scaling approaches to complete species extrapolation for orally encountered toxicants (EPA, 2011a). Consistent with guidance for AEGLs (NRC, 2001), interspecies adjustment via default methods established for RfC derivation (U.S. EPA, 1994) and for oral RfD development (U.S. EPA, 2011a) are not recommended for PALs development.

Physiologically-based pharmacokinetic (PBPK) models have become more useful in eliminating some aspects of uncertainty regarding dosimetry issues, perhaps most frequently in quantifying the variability between test species and humans regarding toxicant exposure at the tissue level (pharmacokinetics, toxicokinetics). Available PBPK models that satisfy requirements of available guidance regarding their application in quantitative risk assessment (e.g., WHO, 2010; U.S. EPA, 2006b, 2014) may be used to assess animal to human (species) variability regarding the uptake of chemicals, doses to target tissues, and time-course for absorption, distribution, and excretion of a chemical of concern and its metabolites. If PBPK modeling is applied, the results should be presented and interpreted in a manner consistent with available guidance (e.g., U.S. EPA, 1994, 2014; WHO, 2010). The results should be presented as dose (mg/kg) or concentration (ppm or mg/m^3) adjusted for animal-to-human toxicokinetic differences. Quantitation of toxicokinetic variability should result in a reduction of the 10-fold default value for the uncertainty factor for interspecies extrapolation (UF_A).

Recently, the U.S. EPA (2014) published guidance for development of data-derived extrapolation factors, which addresses both toxicokinetic (TK) and toxicodynamic (TD) components of inter- and intra-species variability. However, the utility of the more complex approaches for (particularly) inhalation exposure are limited by lack of data for many of the parameters, or by lack of methodology validation. Some of these approaches may also require resources of time and data that preclude their application to chemicals for which emergency response values are a priority. Thus, in the interest of consistency among values under development, their application in PAL value derivation is generally discouraged (but not precluded). This position is consistent with NRC (2001, page 71) regarding UF_A, as evidenced in several statements including: "The guidance (NRC, 1993) suggests that the UF should be based on the quality of the data available," "As data are available, the NAC/AEGL Committee uses data-derived interspecies UFs" and "As always, all information on the chemical, its mechanism of action, structurally related chemical analogs, and informed professional judgement will be used when determining appropriate UFs and evaluating the resultant AEGL values."

An interspecies UF of less than 10 (the historical default value) may be applied if a human equivalent dose or human equivalent concentration can be determined via PBPK modeling, if data for the most sensitive species are used, if humans are shown to be less sensitive than animals, or if the mechanism of toxicity or mode of action (e.g., direct-contact irritation) is not expected to differ between animal species and humans. For direct-contact irritants, a default UF of 3 is appropriate and justified (based on a mode of action that may be assumed to be similar between animals and humans; NRC, 2001) whereas for systemic effects, a UF of 10 may be appropriate. Metabolism and disposition may exhibit interspecies variability indicating that humans are notably less susceptible than rodents, thereby dictating an interspecies UF that is

operationally less than 1. Such is the case for some volatile organic solvents such as chloroform and carbon tetrachloride (Delic et al., 2000; Paustenbach et al., 1986 a,b, 1988; Gargas et al.,1989). Regardless of the method(s) used for quantitation or estimation, the value applied for UF_A should be explained.

5.4.2 Intraspecies variability uncertainty factor (UF_H)

Another major area of uncertainty involves human individual variability (the distribution of effects among humans). Extrapolation of findings to cover the population entails considerations of differences in exposure to chemicals in environmental media and differences in response. Variability in response development among humans, once exposed, can be based on differences in internal dosimetry (toxicokinetics) or differences in the development of the biological response (toxicodynamics). Preexisting physiological conditions (e.g., asthma or other respiratory disorders), age (elderly and infants may exhibit variability in toxic responses relative to other age groups), sex, ethnicity/race, nutritional status, lifestyle habits (smoking and alcohol consumption), and socioeconomic factors may impart sensitivity (susceptibility) through alterations of toxicokinetic or toxicodynamic mechanisms.

Using the normal distribution type as an example, with dose or concentration increasing across the X-axis and frequency of the response among the population increasing up the Y-axis, the bell-shaped profile demonstrates that the frequency or responses is lower at the lower concentrations, that the bulk of the population demonstrates the response as the dose or concentration increases, and that a low proportion of the population may not demonstrate the response until much higher doses or concentrations are attained. Likewise, at a given dose or concentration sufficient to cause the response at some fraction of the population, it is likely that some fraction of the population may demonstrate a response of lesser severity (or none at all), while some other segment of the population may demonstrate a response of greater severity.

UF_H is applied to account for toxicokinetic and toxicodynamic variations among the human population; the default value of 10 is applied when the POD is not determined in humans. When the POD is determined in humans, values other than 10 may be considered. This UF is applied when the toxicity database may not include effects in sensitive populations. An intraspecies UF of less than 10 (the historical default value) may be used if the POD is determined in humans that are representative of population groups presumed to be sensitive (in individuals sensitive to particular compounds such as asthmatics exposed to irritant gases); or if the mechanism of toxicity or mode of action (e.g., ocular, nasal, or pulmonary irritation) is not expected to differ greatly among individuals. Similar to UF_A, a default UF of 3 for UF_H is appropriate and justified for direct-contact irritation (and pulmonary irritation) whereas a UF of 10 for systemic effects may be appropriate.

Reduction of the default value of 10 for UF_H for direct-acting irritants is supported by studies with healthy individuals and asthmatics that indicate a range in variation of 1-5-fold (Table 1). This reduction is also more relevant in derivation of acute and short-term PAL-1 values (for non-irritant chemicals) if uptake and metabolism/disposition differences and tissue accumulation are not expected to vary among individuals in the population. For example, it is documented that the degree of CNS depression caused by volatile organic solvents vary little among age groups in humans (Gregory et al., 1969; de Jong and Eger, 1975). Non-default values for UF_H should be developed and described on a case-by-case basis.

Table 1. Variability in Response of Asthmatics to Irritant Gases

Chemical	Estimated threshold in healthy subjects	Estimated threshold in susceptible subjects	Estimated differential response factor	Susceptible group	Reference(s)
Chlorine	1.0 ppm (P) 1.0 ppm (S)	0.5 ppm (P) 0.5 ppm (S)	2 (P) 2 (S)	Asthmatics People with a history of allergic rhinitis	D'Alessandro et al., 1996; Rotman et al., 1983
Formaldehyde	$\geq$3.0 ppm (P) 2.0 ppm(S)	> 3.0 ppm (P) < 3.0 ppm (S)	Approx. 1 (P) Approx. 0.67 (S)	Asthmatics	Sander et al., 1987
Nitrogen dioxide	1.0 ppm (P)	0.2- 0.3 ppm (P)	3-5	Asthmatics	Hackney et al., 1978
Ozone	0.25 ppm (P)	0.12 ppm (P) <0.24 ppm (P) >0.25 ppm (P) 0.12 ppm (P) 0.25 ppm (P)	2 1 1 2 1	Asthmatics People with COPD People with Ischemic Heart Disease African Americans Gender	Horstman et al., 1995; Bedi et al., 1982
Sulfur dioxide	0.75-1.0 ppm (P)	0.25 ppm (P)	3-4	Asthmatics	Stacy et al., 1981; Bethel et al., 1985
Sulfuric acid	500 ug/m^3 (P)	400 ug/m^3 (P) 100 ug/m^3 (P)	1.3 5	Adult Asthmatics Adolescents Asthmatics	Utell et al., 1982; Koenig et al., 1993; Morrow et al., 1994

P = Pulmonary Function Measurements, S = Symptoms of respiratory distress

PALs are not intended to protect hypersensitive individuals. In the context of PAL development, hypersensitive individuals are those that may demonstrate responses that are extreme and unpredictable based on the range of responses expected from normal characteristics of the general population (e.g., specific age group susceptibilities; common diseases/maladies such as asthma, liver disease, heart disease). In this regard, the application of UF_H is consistent with application in other risk systems (e.g., development of Oral RfD values). Differences in susceptibility among humans based on determinants of exposure to environmental media containing contaminants (e.g., age-dependent variation in rates of drinking water ingestion) can be used to adjust PALs values, when it can be determined that such individuals may be present in the populations exposed. This is covered in section 5.7.3.

5.4.3 Temporal Extrapolation Uncertainty Factor (UF_T)

Once adjusted for temporal considerations, if necessary (see section 5.3.5), additional considerations may be necessary to account for uncertainty introduced by differences between the duration of experimental dosing or exposure and the targeted PAL duration. This can be addressed by developing a numerical value for UF_T. Historically (Dourson, 1994; Dourson et al., 1992; U.S. EPA, 1994), a default value of 10 was applied for UF_S ("Subchronic;" corresponding to UF_T, for "time" within the PALs nomenclature) when extrapolating the results from a subchronic study to develop a reference value for the chronic, lifetime exposure duration. A value of greater than 1 for UF_T may be relevant to derivation of PAL values where experimental

exposure durations are less than the specific PAL duration, e.g. when a critical effect and POD value are identified from an experimental dosing or exposure duration of three days and used to derive a 30-day PAL.

Consideration of the biological endpoint is important – guidance elsewhere in this document (and in NRC, 2001) addresses the dependence of irritant effects (a tier 1 effect) to generally be based on the oral dose or exposure concentration more so than on dosing or exposure duration, and advises against duration extrapolations (either by Haber's law or the ten Berge approach) for irritant effects. This consideration may be extended from consideration of the 8-hour duration for AEGLs to the 24-hour duration, as well. Empirical evidence for the chemical, as well as data describing the temporal relationship of the effect for other chemicals should be considered when deriving a value for UF_T. When the endpoint is not anticipated to increase in severity with respect to duration of exposure (as for irritant effects), a value of 1 for UF_T may be justified.

A value of less than 1 can also be applied for UF_T when data from a life-time animal study are used to derive a longer-term PAL value, which is less than a life-time human dosing or exposure. As discussed by Jarabek (1995), in some instances, where the results from a longer-term study may identify a POD value used to derive a PAL value for a shorter duration (e.g., a POD derived for a tier-appropriate effect from a 28-day study used to derive a 24-hour PAL value), the dose might represent an overly conservative point-of-departure, when applied to a shorter duration. This may occur when the critical effect observed following the full term of the study would not be expected during the first day of exposure (or when the effect observed in a 6-month study might not be expected to occur as a result of a 30-day exposure). For example, gastric lesions resulting from multiple low-level oral exposures to a corrosive agent would not be as likely following a single dose. In this case, the value selected for UF_T should not result in a dosing or exposure (or POD) value below that expected to produce the observed effect at the magnitude of expression at the shorter duration, given the constraints of biological plausibility (or as demonstrated by any empirical evidence for the chemical).

Values higher than 1 should not be considered for the purposes of an uncertainty factor-based adjustment of points of departure for experimental dosing or exposure durations longer than the targeted PAL duration.

5.4.4 Severity Adjustment Uncertainty Factor (UF_S)

This factor has a value higher than 1 when the effect chosen to operationally derive the given POD represents a higher tier; this is primarily applicable in the development of PAL-1 values. PAL-1 values are doses or exposures, above which changes from baseline of specific biomarkers of physiological responses could have adverse health effects. PAL-2 and PAL-3 values are doses or exposures for which adverse health effect, including lethality, may be expected. When dose or concentration response data for effects pertinent to a PAL's tier are not available, the POD for an effect of an increased severity tier may be considered, pending the application of some adjustments. A severity UF may be appropriate if the effects at the POD are more severe (e.g., tier 2 effects) than those defining the targeted PAL tier (e.g., tier 1). The default UF of 10 is generally applied if the effects at the POD are considered severe for the targeted PAL tier. For example, when a POD value for tremors (a PAL-2 effect) is used to derive a PAL-1 value, the value for UF_S would be 10. If, however, the POD is for an effect that may be considered minor within the suite of effects for the higher PAL tier (i.e., of minimal severity), a reduced value of 3 would be considered appropriate for UF_S. A hypothetical example of this circumstance might be observations of histologic changes in the nasal passages of inhalation-exposed rats were characterized using vaguely descriptive terms not conveying an extent of injury rising to the level

of a functional impairment and not indicating that grossly observable lesions occurred that, and for which post-exposure observations necessary to confirm reversibility/irreversibility were not available. Under these circumstances (effect not quantitatively described, without apparent physical/gross changes, apparently not impacting function, and for which data for other chemicals may demonstrate a likelihood of reversibility), such an effect might be justified as a tier 2 effect of minimal severity.

When the critical effect is consistent with the PAL tier definition (e.g., a nonlethal effect is selected as the POD for PAL-3 development), a value of 1 should be applied. An analogy to the contemporary definition and application of UF_L (the LOAEL to NOAEL uncertainty factor) as applied in RfD or RfC derivation may be appropriate

Alternately, PAL values for a given tier may be derived on the basis of values for a lower tier, on a case-by-case basis. This involve a discussion regarding the dose- or exposure-response relationship (i.e., steepness of the dose- or exposure-response curve) if such data are available.

5.4.5 Modifying Factor (MF)

The MF value is specific to the PAL value being derived; the same value for the MF is not applied to all PAL values for the chemical, unless uniquely justified for each value. The modifying factor (MF, with possible values of 1, 3, or 10) is intended to account for scientific uncertainties in the study or database for the PAL value being derived that are not accounted-for in the application of UFs, when those uncertainties exist. When those uncertainties do not exist, or have been accounted-for by the application of UFs, the value for MF is set to 1. The value for the MF depends on professional judgment and chemical-specific science-based assessment. For example, when data deficiencies such as poorly or non-defined critical effects, absence of dose- or exposure-response information, stand-alone toxicity data (e.g., a single LC50 in only one species), or toxicity data for an extremely limited dosing or exposure duration (e.g., 5 minutes) are identified for a targeted PAL value, science-based judgment should be used to evaluate their significance and assign a MF value of 3 or 10.

In PAL application, the MF should be distinguished from the Database Uncertainty Factor (UF_D) as applied (e.g.) in the derivation of RfD and RfC values. Because RfD and RfC values are developed to ensure the safety of the entire population under an assumed continuous exposure for a lifetime, and because these values are often used as the basis for regulatory standards, the toxicity database should be as complete as possible. Thus, quantitation of the value for UF_D should include a consideration of the completeness of the toxicity database to address specific health endpoints (e.g., reproductive toxicity, neurotoxicity, developmental toxicity). In contrast, emergency exposures may involve only a small number of individuals, dosed or exposed for less than a lifetime. In addition, because PAL values are not intended to serve any regulatory function, the adoption of nomenclature for another risk system without also adopting the requirements determining its numerical value would induce confusion.

5.4.6 Multiplication of Uncertainty Factors

UF values are multiplied together such that $10 \times 10 = 100$. In the development of PAL values, when a default value of 10 is reduced by half, it is reduced to one-half an order of magnitude, or to 3.16. This is rounded to a value of "3" for ease of presentation. The multiplication of two values of one-half order of magnitude, each presented as "3," results in a product of "10," the result of multiplying two values of a half order of magnitude. This approach will be used in the application of UFs for development of PAL values and is documented as an accepted

practice in risk assessment (Dourson et al., 1996; Renwick and Lazarus, 1998; NRC, 2001). Also, for simplicity, 3 × 10 = 30.

5.5 Computation of PAL Values

PAL values are computed following identification of the critical effect, identification of the point of departure, duration-adjustment of the point of departure (when necessary), and identification and application of values for the uncertainty factors and modifying factors. PAL values are computed according to:

PAL Value = duration-adjusted POD / (UF x MF)

If the duration-adjusted POD value is 71 mg/kg, and if UF_A = 3; UF_H = 3, UF_T = 1; UF_S = 1, and MF = 1, then the PAL value would be derived as:

71 mg/kg-d / (3 × 3 × 1 × 1 × 1) = 71 mg/kg-d/10 = 7.1 mg/kg-d

5.6 Weight-of-Evidence and Confidence

PALs should be developed within the context of the overall data pertinent to the specific PAL tier. This will entail, in part, selection of a critical effect appropriate for the given PAL tier as well as an appropriate POD. The robustness of the data will ultimately affirm assumptions/judgments utilized in PAL development, and also dictate areas of uncertainty. Much of the weight-of-evidence analysis will be implicit in the course of PAL development. Focal areas may include species variability, dose- or exposure-response relationships, relation of PALs to other dosing or exposure duration data, continuum of effects, mechanism of action, etc. Such analysis allows assessment of reasonableness of the PALs. For example, overly conservative acute exposure PALs will be recognizable as such if they are lower than long-term doses or exposures causing notably less severe effects (see section 5.10).

Supporting studies are used to support the toxicological findings and values obtained from the key study. Findings from supporting studies may also be incorporated into "weight-of-evidence" considerations and may be used to justify the values for some uncertainty factors.

The evaluation of data deficiencies and research needs is also a reflection of the confidence in the PAL values. Those making use of PAL values (emergency planners, emergency responders, etc.) have expressed a critical need for dosing or exposure values and that, in some cases, values with low confidence are better than no value. PAL values will be developed only when data and scientific judgment warrant the derivation of values. Where data sets are limited, scientific judgment may be used to avoid a no-value situation. Logically, PAL values with no confidence will not be developed. Confidence in PAL values will generally be reflected by the magnitude of uncertainty adjustments and the rationales for these adjustments. Assessment and comments on confidence should accompany the PAL values.

5.7 Presentation of Values

PAL values should be presented in units of dose or concentration pertinent to oral and inhalation exposures, respectively. Because the only exposure medium for inhalation exposures is air, PAL values for inhalation exposures should be presented in units of ppm and mg/m3. However, because oral exposures may be based on the ingestion of environmental media such as soil or drinking water, oral PAL doses (mg/kg-d) can be translated into units of concentration in

environmental media on the basis of reliable data and methods.

Oral PAL values may be applicable to several environmental media, including drinking water and soil ingestion. The conversion from an oral PAL dose (mg/kg-d) into corresponding media concentrations (e.g., mg chemical/L drinking water, µg chemical/kg soil) can be accomplished using values for key parameters available from reliable sources. Selection and specification of the data used for oral ingestion parameters should be in accord with general applicability of PAL values and on the basis of the demographics of the population anticipated to be exposed. Values for drinking water ingestion rates and soil ingestion rates are available from a variety of sources (e.g., U.S. EPA, 2011b).

5.7.1 Level of Precision

All PAL values will be expressed as two significant figures. As necessary, rounding toward [+infinity] (nearest up) will be applied (e.g., 2.657 will become 2.7; 0.00244 will become 0.0024; 0.00245 will become 0.0025). Rounding of value to the required two significant figures will be limited to the final PAL value. To retain precision, rounding should not be performed within the calculation cascade. From the example above, the oral PAL value of 248.5 mg/L would be rounded to 250 mg/L.

5.7.2 No PAL Value Established

If pertinent data for a chemical are insufficient and no surrogate chemical, data, or PAL values can be identified, PAL values will not be derived. In this case, the reason(s) for not developing a PAL value will be presented and the term "Not Recommended" (NR) will be presented.

5.7.3 Values for Susceptible Population Groups

The critical effect is communicated for PAL values; when the critical effect is demonstrated in human population groups presumed to be susceptible, or in test animals assumed to represent the characteristics of the human population group presumed to be susceptible (e.g., developing fetal animals or young animals), this should be communicated. Should a child-specific oral PAL value be required for a drinking water exposure scenario, the oral PAL value (in units of mg/kg-d) can be translated into a drinking water concentration by the user on the basis of reliable information such as in the Exposure Factors Handbook (U.S. EPA, 2011b).

5.8 Surrogate Chemicals, Surrogate Data, Surrogate PAL Values

For some chemicals of concern, insufficient data may preclude development of some or possibly all PAL values. PAL values may be based upon professional judgment with the assumption that such judgment will be preferable to a no-guidance situation for responders and end-users. A conscientious effort should be made to develop PALs using structure-activity relationships or other scientifically defensible analogies such as accepting dose response data or PAL values for chemicals justified as surrogates (e.g., Wang et al., 2012) while applying appropriate science-based rigor. Data that may be relevant to PAL development may include chemical-specific information regarding metabolism and disposition, interaction with other chemicals, unique physical-chemical properties, and degradation products. Quantitative structure activity relationship (QSAR) models may also be used to augment sparse data on a specific chemical. The development of newer predictive toxicity tools and data such as those available through high throughput screening offers additional benefit in refining the accuracy of predictive efforts based on structural similarity among chemicals (Berggren et al., 2015).

NRC (2001) also suggested quantifying an AEGL-2 value by selecting a one-third reduction of the AEGL-3 *value* (not the AEGL-3 POD). For example, if data are unavailable with which to empirically derive a value for PAL-2 and the dose- or exposure-response relationship for the chemical of concern is steep (i.e., marked change in response severity with a small change in exposure concentration or dose), the PAL-2 value may be estimated by a one-third reduction of the respective PAL-3 (not by basing the PAL-2 on a one-third reduction of the PAL-3 POD; see NRC, 2001, page 43). Assessment of the steepness of the dose- or exposure-response curve would require dose or exposure response data for minor effects (less than tier 2 severity) as well as lethality data. Such relational data would be necessary to justify using a fractional reduction of a PAL-3 value to estimate the PAL-2 value for the same duration. This approach may also be justified for derivation of PAL-1 values on a case-by-case basis. Justification should include consideration of the nature, strength, and consistency of the data describing the type of responses observed for other PAL tiers at the duration of interest; and the type of responses observed for other durations at the tier of interest.

5.9 Carcinogenicity as a Critical Effect

Carcinogenicity may be most characteristic of a tier 2 response; the likelihood of a carcinogenic response decreases and the uncertainty in predictions of cancer risk increase with decreased dosing or exposure durations (NRC, 2001). However, it is possible that cancer can result from short or single exposures to some carcinogens. Historically, cancer risk has been evaluated based upon continuous, life-time dosing or exposure in laboratory animal studies or from clinical or epidemiologic studies of long-term human exposures. Although the NRC (1993, 2001) has identified cancer as a potential health effect possibly associated with short-term inhalation exposures to certain chemicals, no U.S. federal or state regulatory agency has established regulatory limits for single short-term (≤24 hours) exposure based upon carcinogenicity (NRC, 2001). Extrapolating lifetime cancer risks to shorter durations is possible (e.g., for AEGLs; NRC, 2001) and may be valuable in some emergency response planning situations, but doing so requires the communication of certain caveats and the acknowledgement of some inherent uncertainties.

Additional considerations include the possibility of unnecessary risk and resource allocations associated with some health-protective emergency response actions (e.g., evacuations) that may be undertaken on the basis of estimations of risk embodying uncertainty and inherent health conservatism, as well as the potential for realizing a relatively low predicted incidence of effects among a potentially small exposed population. It should be understood that cancer risk assessment is an inherently conservative endeavor, usually including linear low-dose extrapolation methods in the absence of confirmatory data. This is done both for chemicals whose carcinogenic mode of action is based on a direct interaction with DNA and for chemicals for which the mode of action is not known to involve a direct interaction with DNA. Also, because most of the available cancer risk values have been developed on the basis of findings from chronic dosing or exposure of experimental animals, the carcinogenic risk from shorter durations of oral dosing or inhalation exposure has received less attention, and so is less certain than that from chronic dosing or exposure.

While the extrapolation of lifetime cancer risks to durations of dosing or exposure much shorter than a lifetime can be completed in the estimation of emergency response guidance levels (NRC, 2003), the level of uncertainty in such risk estimates generally increases with decreased dosing or exposure durations. For PALs, this means that the level of uncertainty in carcinogenic risk for PAL durations will increase with decreasing PAL duration. In fact, in considering the

application of cancer risk assessment approaches in the development of AEGL values, NRC (2001) seems to advise caution in developing risk estimates that may impart a higher level of conservatism (e.g., as might occur when based on cancer risk). With respect to sulfur mustard, NRC (NRC, 2003) indicated, "The use of excess-cancer-risk estimates in setting AEGL values was precluded by the uncertainties involved in assessing excess cancer risk following a single acute exposure of 8 hr or less, the relatively small population dosed or exposed during an accidental or other emergency situations, and the potential risks associated with evacuations."

Whether cancer risk should receive additional attention relative to identifying a POD for PALs development should be revisited as cancer risk methods advance into this area and/or when data from carcinogenicity studies reporting the results of acute, single-dose or short-term dosing or exposure of test species or humans become available which support such an evaluation.

A quantitative carcinogenicity assessment should be performed only when a U.S. EPA cancer classification and slope factor/unit risk are available. Data from reliable sources including reports from controlled cancer bioassays in laboratory animals, genotoxicity studies, human epidemiologic studies, and human accidental dosing or exposure reports will be evaluated. Criteria typical for evaluation of animal bioassays (e.g., numbers, species, and strains of animals, dose groups, dosing or exposure duration, tumor type/incidences) and epidemiologic studies (methods, confounders, statistical analysis of responses, etc.) will be applied to help determine the relevance of specific studies. To assess carcinogenic risk potential, NRC guidance (NRC, 1986; 1993; 2001) and U.S. EPA guidelines (U.S. EPA, 2005a, 2005b) should be followed.

Although a cancer assessment should be conducted for completeness if a U.S. EPA cancer classification and slope factor or unit risk value are available, it should be presented in an appendix to the Technical Summary Document. Any PAL value derived based on carcinogenicity should not be recommended as the quantitative basis for establishing a PAL value, given the intended application of PAL values as decision aids during and following emergency events. Rather, the observed irreversible effect or effect impairing the ability to escape a contaminated source or atmosphere should be used as the basis for PAL-2 values.

5.10 Final Adjustment of PAL Values

Although the derivation of PAL values follows well-developed guidelines for data analysis, selection of an appropriate key study, POD, UF application, and dose or exposure concentration-duration adjustments, resulting PALs may be occasionally inconsistent with known human experience. This may occur for several reasons including the selection of UF values; the differential basis of PAL values for a given duration or severity level on observations in humans versus animals; the extent to which experimental observations from one duration to another are adjusted, normalized or justified for application to a PAL value of another duration, etc. Science-based judgment will be applied to justify a quantitative adjustment in the final PAL value(s). It is not recommended that this adjustment be applied through manipulation of the UF. Rather it should be clearly stated as a final change in the PAL value(s) based upon a comparison of the PAL with human experience information and an overall evaluation of the reasonableness of the original and adjusted PAL value(s).

If the PAL is found to be in conflict with available human data, adjust the PAL and clearly explain the basis of the adjustment. Essentially, this might be necessary where accepted methodology is applied but results in unrealistic values. As cautioned by NRC (2001), the establishment of overly conservative guideline (AEGL) values may result in health protective activities and actions that may, themselves, have consequences. Overly protective PALs may

drain resources and create undue hardships on affected communities such as increased incidence of traffic accidents and injuries during unnecessary evacuations and delayed reentry.

6 Chemical Considerations

6.1 Complex Mixtures/Concurrent Exposure Issues

It is likely that situations necessitating the use of a PAL may involve concurrent exposure to other chemicals, exposures to simple mixtures of chemicals (mixtures with few components) or exposure to complex mixtures (mixtures with many components). It may be assumed that in situations where exposure involves more than one specific chemical, the most protective PAL (i.e., chemical with the lowest PAL) will dictate on-scene responses. Considerations may include the specific mechanism of action of the individual components and the persistence of the chemicals in the environment. The evaluation of additive, potentiated, or synergistic effects may be important. While the management of risks associated with concurrent chemicals might depend more heavily on the expertise of on-scene risk managers, any development of PALs for a chemical mixture not based on empirical data for the mixture itself should involve personnel with mixtures toxicology skills and/or mixtures risk assessment skills.

6.2 Degradation Products

For some chemicals, and in some circumstances, it may be valuable to also consider the toxicological contribution of degradation products in the assessment (Wang et al., 2012). Consideration should be given to the availability of data for the degradation product regarding its identification and quantitation, the environmental factors affecting its formation, its rate of formation, the nature of its effects, and the relationship of those effects to dose. Knowledge of the release time, rate of formation and toxic properties of degradation products represent important sources of information when estimating the value of assessing the risks of degradation products. For example, if degradation products are formed slowly over time, dosing or exposure to degradation products may not be a priority concern for acute or short-duration dosing or exposure, but might be a concern when dosing or exposure involves a previous release (e.g., during remediation of a previously contaminated site).

If it is known that degradation products will possess toxicity similar to or greater than the parent compound, development of PAL values for these products will be independent of the parent chemical. PAL documents for degradation products and the parent chemical should be cross-referenced. In addition to relative toxicity to the parent compound, attention (in the context of a combined dosing or exposure i.e., a mixtures toxicity issue) should be given to the relative contribution of any noteworthy degradation product, as well as to its environmental persistence, to the overall response (e.g., a degradation product of significant toxicity may occur in only very small quantities).

7 Research Needs/Recommendations

Data deficiencies will be characterized as precisely as possible for every PAL document where it was not possible to derive scientifically defensible PALs. Based upon the identified deficiencies, recommendations will be made regarding generation of required data and studies that would improve the quality and reduce uncertainties in the PAL document. This may include suggestions/input regarding experimental protocols for specific type of studies.

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