Current Intelligence Bulletin (CIB): Derivation of Immediately Dangerous to Life and Health (IDLH) Values

National Institute for Occupational Safety and Health, 2010

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Foreword

Since the establishment of the original Immediately Dangerous to Life and Health (IDLH) values in 1974, the National Institute for Occupational Safety and Health (NIOSH) has continued to review available scientific data to improve the protocol used to derive the acute exposure guidelines, in addition to the chemical-specific IDLH values. The primary objective of this Current Intelligence Bulletin (CIB) is to present a protocol, based on the modern principles of risk assessment and toxicology, for the derivation of IDLH values that characterize the health risks of occupational exposures to high concentrations of airborne contaminants. The new protocol for deriving IDLH values incorporates the methodology established by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances—consisting of members from the U.S. Environmental Protection Agency (EPA), the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation, other federal and state governments, the chemical industry, academia, and other organizations from the private sector—during the derivation of community-based acute exposure limits called Acute Exposure Guideline Levels (AEGLs). The inclusion of the AEGL methodology has helped ensure that the IDLH values derived using the guidance provided within this document are based on validated scientific rationale.

The intent of this document is not only to update the protocol used by NIOSH to develop health-based IDLH values, but to also increase the transparency behind their derivation. We hope that the increased transparency will provide occupational health professionals additional information that can be applied to improve the characterization of the hazards of high concentrations of airborne contaminants and result in a more informed decision process for the selection of respirators, establishment of Risk Management Plans for non-routine work practices and Emergency Preparedness Plans capable of better protecting workers.

John Howard, M.D.

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Director, National Institute for Occupational Safety and Health

Centers for Disease Control and Prevention

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Executive Summary

Chemicals are an ubiquitous component of the modern workplace. Occupational exposures to chemicals have long been recognized as having the potential to adversely affect the lives and health of workers. Acute or short-term exposures to high concentrations of some airborne chemicals have the ability to quickly overwhelm workers, resulting in a wide spectrum of undesirable health outcomes that may include irritation of the eyes and respiratory tract, severe irreversible health effects, impairment of the ability to escape from the exposure environment and, in extreme cases, death. Airborne concentrations of chemicals capable of causing such adverse health effects or impeding escape from "high risk" conditions may arise from a variety of non-routine workplace situations affecting workers, including special work procedures (e.g., confined-spaces), industrial accidents (e.g., chemical spills or explosions), and chemical releases into the community (e.g., during transportation incidents or other uncontrolled release scenarios).

Since the 1970s, the National Institute for Occupational Safety and Health (NIOSH) has been responsible for the development of acute exposure guidelines called immediately dangerous to life or health (IDLH), which are intended to characterize these "high risk" conditions. Used as a key component of the NIOSH *Respirator Selection Logic* [NIOSH 2004], the intended purpose of establishing an IDLH value is (1) to ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment and (2) is considered a maximum level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted. In addition, occupational health professionals have employed these acute exposure guidelines beyond their initial purpose as a component of the NIOSH *Respirator Selection Logic*. Examples of such applications of the IDLH values include the development of Risk Management Plans (RMPs) for non-routine work practices governing operations in "high risk" environments (e.g., confined spaces) and the development of Emergency Preparedness Plans (EPPs), which provide guidance for emergency response personnel and workers during unplanned exposure events.

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Since the establishment of the IDLH values in 1970s, NIOSH has continued to review available scientific data to improve the protocol used to derive the acute exposure guidelines, in addition to the chemical-specific IDLH values. The information presented in this Current Intelligence Bulletin (CIB) represents the most recent update of the scientific rationale and protocol used to derive IDLH values. The primary objectives of this document are:

1. To provide a brief history of the development of IDLH values,
2. To update the scientific bases and risk assessment methodology used to derive health-based IDLH values based on quality toxicity and human health effects data,
3. To provide transparency behind the rationale and derivation process for IDLH values, and
4. To demonstrate how scientifically-credible IDLH values can be derived based on available data resources.

The updated protocol outlined in this CIB reflects the modern principles and understanding in the fields of risk assessment, toxicology and occupational health and provides the scientific rationale for the derivation of health-based IDLH values. According to this protocol, IDLH values are based on health effects considerations determined through a critical assessment of the toxicology and human health effects data. This approach ensures that the IDLH values reflect an airborne concentration of a substance that represents a “high risk” situation that may endanger workers’ life or health. The emphasis on health effects is consistent with both the traditional use of IDLH values as a component of the respirator selection logic and the growing applications of IDLH values in RMPs for non-routine work practices governing operations in “high” risk environments (e.g., confined spaces) and the development of EPPs. Incorporated with the updated protocol are the standing guidelines and procedures used by the U.S. Environmental Protection Agency (EPA), National Academies of Science (NAS) and the Agency for Toxic Substance and Disease Registry (ATSDR) for the development of community-based acute exposure limits called Acute Exposure Guideline Levels (AEGLs). The inclusion of the AEGL methodology has helped ensure that the health-based IDLH values derived using the guidance provided within this document are based on validated scientific rationale.

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The updated protocol is based on a weight-of-evidence approach that applies scientific judgment for the critical evaluation of the quality and consistency of the scientific data, and in extrapolation from the available data to the IDLH value. The weight of evidence approach refers to the critical examination of all the available data from diverse lines of evidence and the derivation of a scientific interpretation based on the collective body of data including its relevance, quality and reported results. This is in contrast to a purely hierarchical or strength of evidence approach that would use rigid decision criteria for selecting a critical adverse effect, a point of departure (POD) or the point on the dose-response curve from which dose extrapolation is initiated, and applying default uncertainty factors (UFs) to derive the IDLH value. Conceptually, the derivation process for IDLH values is similar to that used in other risk assessment applications including the process steps of:

- Hazard characterization,
- Identification of critical adverse effects,
- Identification of a POD,
- Application of appropriate UF based on the study and POD, and
- Determination of the final risk value.

However, rather than narrowing the analysis to a single study because of the limited data available on many substances, the weight-of-evidence approach, which is more integrative, is used to develop the IDLH value based on consideration of alternatives and different lines of evidence. In particular, application of the appropriate UF to each potential POD allows for consideration of the impact of the overall dataset as well as the uncertainties associated with each potential key study in determining the final IDLH value.

The primary steps (*see Figure 3.0*) applied in the establishment of an IDLH value include the following:

- Critical review of human and animal toxicity data to identify potential relevant studies and characterize the various lines of evidence that can support the derivation of the IDLH value;

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- Determination of a chemical's mode of action (MOA) or description of how a chemical exerts its toxic effects;
- Application of duration adjustments (time scaling) to determine 30-minute equivalent exposure concentrations and conduct of other dosimetry adjustments as needed;
- Selection and application of a UF for POD or critical adverse effect concentration identified from the available studies to account for issues associated with inter- and intraspecies differences, the severity of the observed effects, data quality or data insufficiencies; and
- Development of the final recommendation for the IDLH value from the various alternative lines of evidence using a weight of evidence approach with all of the data.

NIOSH recognizes that in some cases a health-based IDLH value might not account for all workplace hazards, such as safety concerns or considerations. Situations and conditions that might preclude the use of a health-based IDLH value include, but are not limited to:

- When the airborne concentration of a substance is sufficient to cause oxygen deprivation (oxygen concentration <19.5%), which represents a life-threatening condition;
- When the concentration of particulate matter generated during a process significantly reduces visibility preventing escape from the hazardous environment; or
- When the airborne concentration of a gas or vapor is greater than 10% of the lower explosive limit (LEL) and represents an explosive hazard.

In such cases, it is important that safety hazards or other considerations be taken into account. Information on the non-health based hazards will be incorporated within the support documentation (see *Appendix A*) for an IDLH value to aid occupational health professionals in the development of RMPs for non-routine work practices governing operations in "high" risk environments (e.g., confined spaces) and EPPs. For example, in the event that the derived health-based IDLH value exceeds 10% of the LEL concentration for a flammable gas or vapor the following hazard statement will be included within the support documentation "The health-

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based IDLH value is greater than 10% of the LEL (>10% LEL) of the chemical of interest in air. Therefore, safety considerations against hazard of explosion must be taken into account." In addition, the notation (> 10 % LEL) will appear besides the IDLH value within the NIOSH Pocket Guide to Chemical Hazards [NIOSH 2005] and other NIOSH publications. The use of hazard statements and notations to provide supplemental information on non-health based hazards and considerations aligns with the protocol used to derive the AEGLs.

Supplemental information is included within this CIB to provide interested parties insight into (1) the literature search strategy, (2) the scheme used to prioritize and select chemicals for which an IDLH value will be established and (3) an overview of the analysis applied by NIOSH to develop a scientifically-based approach for the selection of the UF during the derivation of IDLH values. In addition, Appendix A presents an example of the derivation of an IDLH value for vinyl acetate (CAS #108-50-4) based on the scientific rationale and process outlined in this CIB. The example highlights the primary steps within the establishment of an IDLH value including a critical review of the identified human and animal data, discussion of the selection of the POD and UF and extrapolation of the 30-minute equivalent exposure concentration from animal toxicity data.

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Abbreviations and Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
AEGL	Acute Exposure Guideline Levels (published by NRC)
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	biologically based dose response
BMC	benchmark concentration
BMCL	benchmark concentration lower limit
BMD	benchmark dose
BMDS	Benchmark Dose Software (developed by USEPA)
CIB	Current Intelligence Bulletin
Conc	concentration
"C"	ceiling value
CA	carcinogen
Cal/EPA	California Environmental Protection Agency
CAS#	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CFATS	Chemical Facility Anti-Terrorism Standards (developed by DHS)
CFR	Code of Federal Regulations
CHEMID	online chemical identification database (developed by NLM)
CIB	Current Intelligence Bulletin (developed by NIOSH)
CNS	central nervous system
COHb	carboxyhemoglobin
Conc	concentration
DHHS	U.S. Department of Health and Human Services
DHS	U.S. Department of Homeland Security
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy

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DOL	U.S. Department of Labor
DOT	U.S. Department of Transportation
DT	developmental toxicant
EC	effective concentration
EEGL	Emergency and Continuous Exposure Guidance Levels (published by NRC)
EINECS	European INventory of Existing Commercial chemical Substances
EMBASE	online biomedical journal abstract and indexing database (subscription based)
EPP	Emergency Preparedness Plan
ERPG	Emergency Response Planning Guidelines (developed by AIHA)
ERG	Emergency Response Guidebook (developed by DOT)
EU	European Union
FEL	frank effect level
FACA	Federal Advisory Committee Act
GI	gastrointestinal
GLP	Good Laboratory Practices
HAZARDTEXT®	online hazardous substance database (subscription based)
HazMap	online occupational exposure to hazardous agents database (developed by NLM)
HCN	hydrogen cyanide
hr	hour
HPV	high production volume
HSDB	Hazardous Substance Database (developed by NLM)
HSEES	Hazardous Substance Emergency Events Surveillance (developed by ATSDR)
IARC	International Agency for Research on Cancer
ICSC	International Chemical Safety Cards (developed by IPCS)
IDLH	Immediately Dangerous to Life or Health (developed by NIOSH)
i.p.	intraperitoneal injection
IPCS	International Programme on Chemical Safety

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IRIS	Integrated Risk Information System (developed by EPA)
IRR	irritant
ITER	International Toxicity Estimates for Risk database (developed by *TERA*)
JSC	Johnson Space Center (division of NASA)
k	a constant reflected in the equation expressing conc x time relationships
kg	kilogram
L	liter
lbs	pounds
LC	lethal concentration
LD	lethal dose
LEL	lower explosive limit
L/min	liters per minute
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
m^3	cubic meter
MEDITEXT®	online medical and toxicology database (subscription based)
mg/m^3	milligrams per cubic meter of air
mg/m^3-min	milligrams per cubic meter of air per minute
min	minute
MOA	mode of action
MSHA	Mine Safety and Health Administration
NAC/AEGL	National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances
NASA	National Aeronautics and Space Administration
NAS/NRC	National Academy of Sciences/National Research Council
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC2	bibliographic database of NIOSH supported occupational safety and health publications
NJ-HSFS	New Jersey Hazardous Substance Fact Sheets

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NLM	National Library of Medicine
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
OSHAREFS	online occupational safety and health database (subscription based)
PAL	Provisional Advisory Levels (developed by DHS)
PBPK	physiologically-based pharmacokinetic
PEL	Permissible Exposure Limit (developed by OSHA)
ppm	parts per million
POD	point of departure
PUBMED	online biomedical literature citation database (developed by NLM)
RD	respiratory depression
REL	Recommended Exposure Limit (developed by NIOSH and MSHA)
RfC	inhalation reference concentration
RIVM	Netherlands National Institute for Public Health and the Environment
RMP	Risk Management Plan
R-phrases	risk phrases (developed by EU)
RTECS	Registry of Toxic Effects of Chemical Substances
SCAPA	Subcommittee on Consequence Assessment and Protective Actions
SCBA	self-contained breathing apparatus
SCP	Standards Completion Program (developed by NIOSH and OSHA)
SMAC	Spacecraft Maximum Allowable Concentration (developed by NASA, published by NRC)
SPEGL	Short-term Public Emergency Guidance Levels (developed by NRC)
STEG	short-term exposure guidelines

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STEL	Short Term Exposure Limit (developed by ACGIH)
ST	short term exposure limit
TEEL	Temporary Emergency Exposure Limit (developed by DOE)
TERA	Toxicology Excellence for Risk Assessment
TIH	toxic inhalation hazard (developed by DOT)
TLV®	Threshold Limit Value (developed by ACGIH)
TOXLINE	online toxicology literature database (developed by NLM)
TWA	time weighted average
UF	uncertainty factor
USEPA	U.S. Environmental Protection Agency
WEEL	Workplace Environmental Exposure Limits (developed by AIHA)
WHO	World Health Organization

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Glossary[1]

Acute Exposure: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

Acute Exposure Guideline Level (AEGL): Tiered guideline levels for exposures to airborne substances intended to provide estimates of concentrations and exposure durations (minutes to hours) above which one could reasonably anticipate observing effects in the general population ranging from discomfort, irritation, or certain asymptomatic nonsensory effects through more severe effects (depending on the tier).

Acute Reference Concentration (RfC)[2]: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hours or less) exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in USEPA's noncancer health assessments.

Acute Toxicity: Any poisonous effect produced within a short period of time following an exposure, usually 24 to 96 hours.

Acute Toxicity Test: Experimental animal study to determine what adverse effects occur in a short time (usually up to 14 days) after a single dose of a chemical or after multiple doses given in up to 24 hours.

[1] Glossary definitions are from a number of sources unless otherwise noted. These sources include AIHA [2008], Hayes [2008], IUPAC [2007], NAS [1986, 2001], NASA [1999], NIOSH [2005], OSHA [2003], US DHS [2007], US DOE [2008], US DOT [2008].

[2] USEPA definition [USEPA 2010]

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Adverse Effect: A substance related biochemical change, functional impairment, or pathologic lesion that affects the performance of an organ or system, or alters the ability to respond to additional environmental challenges.

Analytical (Actual) Concentration: The test article concentration to which animals are exposed (i.e., the concentration in the animals' breathing zone), as measured by analytical (GC, HPLC, etc) or gravimetric methods. The analytical or gravimetric concentration (not the nominal concentration) is usually used for concentration response assessment.

Assigned Protection Factor (APF): The minimum anticipated protection provided by a properly functioning respirator or class of respirators to a given percentage of properly fitted and trained users. For example, an APF of 10 for a respirator means that a user could expect to inhale no more than one tenth of the airborne contaminant present.

Benchmark Dose/Concentration (BMD/BMC)[3]: A dose or concentration that produces a predetermined change in response rate of an effect (called the benchmark response or BMR) compared to background.

Benchmark Response (BMR): A predetermined change in response rate of an effect. Common defaults for the BMR are 10% or 5%, reflecting study design, data variability and sensitivity limits of the study used.

BMCL[2]: A statistical lower confidence limit on the concentration at the BMC.

[3] USEPA definition [USEPA 2010]

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Biologically Based Dose Response (BBDR) model[4]: A predictive model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

Bolus Exposure: A single, relatively large dose.

Bounding: A process of identifying estimates of exposure, dose, or risk that are clearly higher than, or lower than, the exposure, dose, or risk of interest. Bounding can help to define the practical uncertainty associated with the estimate of a derived risk value, such as an IDLH value.

Cancer Risk: The likelihood of developing cancer given a specific exposure (i.e., during a working lifetime). Individual cancer risks are determined by multiplying a specific exposure (10^{-3} for occupational) by the cancer potency. A 10^{-3} risk level is associated with a 1 in 1,000 chance of developing cancer.

Carcinogen: An agent capable of causing cancer.

Carcinogenicity: Process of induction of malignant tumors by chemical, physical or biological agents.

Ceiling Value ("C"): U.S. term in occupational exposure indicating the airborne concentration of a potentially toxic substance which should never be exceeded in a worker's breathing zone.

[4] USEPA definition [USEPA 2010]

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Chronic Exposure: Repeated exposure for an extended period of time. Typically exposures are more than approximately 10% of life span for humans and >90 days to 2 years for laboratory species.

Concentration (Conc): The mass of test article per unit volume of air (e.g., mg/L, mg/m^3) or the volume of test article per unit volume (e.g., ppm, mL/L).

Critical Study[5]: The study that contributes most significantly to the qualitative and quantitative assessment of risk.

Cumulative Toxicity: Toxicity that is related to the cumulative, or total, dose to an organ or the body of an individual, up to a specified date or time.

Developmental Toxicity[6]: Adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth and functional deficiency.

De Novo: Fresh; over again from the beginning; referring to an analysis that does not build on prior analyses.

Dose[7]: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.

[5] USEPA definition [USEPA 2010]

[6] USEPA definition [USEPA 2010]

[7] USEPA definition [USEPA 2010]

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Concentration-response Curve: Graph of the relationship between the exposure concentration and the incidence or other measure of response of a defined biological effect in an exposed population or animal study.

Dosimetry: Estimating or measuring the quantity of material at specific target sites, determination of respiratory tract region deposition fractions.

ECt_{50}: A combination of the effective concentration of a substance in the air and the exposure duration that is predicted to cause an effect in 50% (one half) of the experimental test subjects.

Emergency Exposure Guidance Levels (EEGL): A ceiling guidance level for unpredicted, single, short-term, emergency exposures (1-24 hr) of a defined occupational group. EEGLs are developed at the request of the U.S. Department of Defense by the National Research Council's Committee on Toxicology.

Emergency Response Planning Guidelines (ERPG): Maximum airborne concentrations below which nearly all individuals can be exposed without experiencing health effects for 1-hour exposure. ERPGs are presented in a tiered fashion with health effects ranging from mild or transient to serious, irreversible or life threatening (depending on the tier). ERPGs are developed by the American Industrial Hygiene Association (AIHA).

Endpoint: An observable or measurable biological event or substance concentration (e.g., metabolite concentration in a target tissue) used as an index of exposure to a substance.

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

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Extrapolation: An estimate of the response at a point outside the range of the experimental data, generally through the use of a mathematical model, although qualitative extrapolation may also be conducted. The model may then be used to extrapolate to response levels that cannot be directly observed.

Fetal Toxicity: An adverse effect occurring in the fetus from exposure to a substance. These effects can occur through direct interaction with the fetus or indirectly from the effects of maternal toxicity.

Gestation: Pregnancy, the period of development in the uterus from conception until birth.

Hazard: A potential source of harm. Hazard is distinguished from risk, which is the probability of harm under specific exposure conditions.

Healthy Worker Effect: Epidemiological phenomenon observed initially in studies of occupational diseases: workers usually exhibit lower overall disease and death rates than the general population, due to the fact that the old, severely ill and disabled are ordinarily excluded from employment. Death rates in the general population may be inappropriate for comparison with occupational death rates, if this effect is not taken into account.

Immediately Dangerous to Life and Health (IDLH) condition: a situation that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment [NIOSH 2004].

IDLH value: (1) a maximum (airborne concentration) level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted; (2) maximum level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted [NIOSH 2004].

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Implantation: The process by which a fertilized egg implants in the uterine lining, typically several days following conception depending on the species.

Inhalation Reference Concentration (RfC)[8]: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in USEPA's noncancer health assessments.

Internal Dose: A dose denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries.

International Toxicity Estimates for Risk Database (ITER): A free internet database of human health risk values and cancer classifications for over 600 chemicals of environmental concern from multiple organizations worldwide.

Intraperitoneal: Within the peritoneal cavity (the area that contains the abdominal organs).

LC_{50}: The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals.

LC_{lo}: The lowest lethal concentration of a substance in the air reported to cause death, usually to a small percentage of the test animals.

[8] USEPA definition [USEPA 2010]

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LD_{50}: The statistically determined median lethal dose of a substance that is estimated to cause death in 50% (one half) of the test animals.

LD_{lo}: The lowest dose of a substance that causes death, usually to a small percentage of the test animals.

LEL: The minimum concentration of a gas or vapor in air below which propagation of a flame does not occur in the presence of an ignition source.

Lethality: Pertaining to, or causing death, fatal; referring to the deaths resulting from acute toxicity studies. May also be used in lethality threshold to describe the point of sufficient substance concentration to begin to cause death.

Lowest Observed Adverse Effect Level (LOAEL): the lowest tested dose or concentration of a substance that has been reported to cause harmful (adverse) health effects in people or animals.

Malignant: A growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body.

Maternal Toxicity: Adverse effects occurring in the mother during a developmental study, typically a result of the high exposure concentrations required for developmental studies. Maternal toxicity can result in adverse effects to the fetus.

Maximum Likelihood Concentration: A statistical estimate of the concentration that was most likely to cause the desired effect.

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Mode of Action: The sequence of significant events and processes that describe how a substance causes a toxic outcome. Mode of action is distinguished from the more detailed mechanism of action, which implies a more detailed understanding on a molecular level.

Nominal Concentration: The concentration of test article introduced into a chamber. It is calculated by dividing the mass of test article generated by the volume of air passed through the chamber. The nominal concentration does not necessarily reflect the concentration to which an animal is exposed.

No Observed Adverse Effect Level (NOAEL): the lowest tested dose or concentration of a substance that has been reported to cause no harmful (adverse) health effects in people or animals.

Occupational Exposure Level (OEL): Regulatory level of exposure to substances, intensities of radiation etc. or other conditions, specified appropriately in relevant government legislation or related codes of practice.

Parturition: The act of giving birth. Reproductive studies are usually scheduled to end before the test animal gives birth.

Peak Concentration: Highest concentration of a substance recorded during a certain period of observation.

Permissible Exposure Limit (PEL): Exposure limits developed by US OSHA (29 CFR 1910.1000) for allowable occupational airborne exposure concentrations. PELs may be designated as ceiling, STEL or TWA limits.

Permit-Required Confined Spaces: OSHA defines a confined space as one that has one or more of the following characteristics: (1) contains or has the potential to contain a

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hazardous atmosphere; (2) contains a material that has the potential to engulf an entrant; (3) has walls that converge inward or floors that slope downward and taper into a smaller area which could trap or asphyxiate an entrant; (4) or contains any other recognized safety or health hazard, such as unguarded machinery, exposed live wires, or heat stress.

Physiologically Based Pharmacokinetic (PBPK) Model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism and excretion.

Point of Departure (POD): The point on the dose-response curve from which dose extrapolation is initiated. This point can be the lower bound on dose for an estimated incidence or a change in response level from a concentration-response model (BMC), or a NOAEL or LOAEL for an observed effect selected from a dose evaluated in a health effects or toxicology study.

Promulgation: To make known (a decree, for example) by public declaration; announce officially.

Provisional Advisory Level (PAL): A tiered set of air and drinking water threshold exposure values for high priority chemical, biological and radiological agents intended for the general public, including susceptible and sensitive subpopulations. Developed by USEPA to inform risk-based decision-making during a response to terrorist or natural disaster incidents.

RD_{50}: The statistically determined concentration of a substance in the air that is estimated to cause a 50% (one half) decrease in the respiratory rate in mice.

Recommended Exposure Limit (REL): Maximum exposure limit to prevent adverse health effects based on human and animal studies and established for occupational (10-hour

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shift, 40-hour week) inhalation exposure developed by NIOSH or MSHA. RELs may be designated as ceiling, STEL or TWA limits.

Reproductive Toxicology: Adverse effects on male and/or female reproductive function, capacity, or associated endocrine system components. Common adverse effects include altered sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that depend on reproductive integrity of the system.

Risk Phrases: A European system of hazard codes and phrases for labeling dangerous substances and compounds, consisting of the letter R followed by a series of numbers. Each number corresponds to a specific hazard phrase. For example R-34 means "causes burns" regardless of any language translations.

Sensory Irritation: Immediate irritation to the eyes and nose, due to an interaction between the substance and receptors in the trigeminal nerve endings. Often an endpoint for OEL derivation because high exposure levels often cause burning and painful sensations.

Short-Term Exposure: Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.

Short-Term Exposure Limit (STEL): A worker's 15-minute time weighted average exposure concentration that shall not be exceeded at any time during a work day.

Short-Term Public Emergency Guidance Levels (SPEGL): A ceiling guidance level for unpredicted, single, short-term, emergency exposures (1-24 hr) for the general public. SPEGLs are developed at the request of the U.S. Department of Defense by the National Research Council's Committee on Toxicology.

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Spacecraft Maximum Allowable Concentration (SMAC): Guideline values set to protect astronauts from spacecraft contaminants. Short-term guidelines (1-24hr) apply to accidental releases and long-term guidelines (up to 180 days) apply to low levels of contaminants aboard a spacecraft. These guidelines are set by the NASA/JSC in cooperation with the National Research Council's Committee on Toxicology.

Surrogate: Relatively well studied chemical whose properties are assumed, with appropriate adjustments for differences in potency, to apply to an entire chemically- and toxicologically-related class; for example, benzo(*a*)pyrene data is assumed to be toxicologically equivalent to all carcinogenic polynuclear aromatic hydrocarbons, or is used as a basis for extrapolating to these other chemicals.

Systemic Concentration: The amount of a substance that is absorbed and distributed throughout the body.

Target Organ: Organ in which the toxic injury manifests itself in terms of dysfunction or overt disease.

Temporary Emergency Exposure Limit (TEEL): Tiered temporary guidance values that are used by DOE until AEGL or ERPG values are available. TEELs are derived by the Subcommittee on Consequence Assessment and Protective Actions (SCAPA) to aid in emergency preparedness hazard analysis of DOE facilities, employees and adjacent communities in the event of an accidental chemical release.

Threshold Limit Value (TLV®): Recommended guidelines for occupational exposure to airborne contaminants published by the American Conference of Governmental Industrial Hygienists (ACGIH). TLVs represent the average concentration in mg/m^3 for an 8-hour workday and a 40-hour work week to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

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Time-Weighted Average (TWA): A worker's 8-hour (or 10-hour) time weighted average exposure concentration that shall not be exceeded at any time during an 8-hour (or 10-hour) work shift of a 40-hour week. The average concentration is weighted to take into account the duration of different exposure concentrations.

Toxic Inhalation Hazard (TIH): Gases or volatile liquids that are known or presumed on the basis of tests to be so toxic to humans as to pose a hazard to health in the event of a release during transportation, determined by DOT.

Toxicity: The degree to which a substance is able to cause an adverse effect on an exposed organism.

Toxicology: Scientific discipline involving the study of the actual or potential danger presented by the harmful effects of substances (poisons) on living organisms and ecosystems, of the relationship of such harmful effects to exposure, and of the mechanisms of action, diagnosis, prevention and treatment of intoxications.

Tumor: An abnormal mass of tissue that results from excessive cell division that is uncontrolled and progressive. Tumors perform no useful body function. Tumors can be either benign (not cancerous) or malignant (cancer).

Uncertainly Factors: Mathematical adjustments applied to the POD when developing IDLH values. The uncertainty factors for IDLH value derivation are determined by considering the study and effect used for the POD, with further modification based on the overall database.

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Weight-Of-Evidence (Toxicity): Extent to which the available biomedical data supports a conclusion, such as whether a substance causes a defined toxic effect (e.g., cancer in humans), or whether an effect occurs at a specific exposure level.

Workplace Environmental Exposure Limits (WEEL): Occupational exposure limits (OELs) for substances commonly used in the workplace that do not already have an OEL. WEELs are developed by AIHA and may be designated as ceiling, short-term STEL or 8-hr TWA limits.

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Chapter 1.0-Introduction

Occupational exposures to chemicals have long been recognized as having the potential to adversely affect the lives and health of workers. Acute or short-term exposures to high concentrations of some airborne chemicals have the ability to quickly overwhelm workers, resulting in a wide spectrum of undesirable health outcomes that may include irritation of the eyes and respiratory tract, severe irreversible health effects, impairment of the ability to escape from the exposure environment and, in extreme cases, death. Airborne concentrations of chemicals capable of causing such adverse health effects or impeding escape from “high risk” situations or conditions may arise from a variety of situations affecting workers, including special work procedures (e.g., confined-spaces) and industrial accidents (e.g., chemical spills or explosions), or chemical releases into the community (e.g., during transportation incidents or other uncontrolled release scenarios).

The "immediately dangerous to life or health air concentration values (IDLH values)" developed by the National Institute for Occupational Safety and Health (NIOSH) characterize these “high risk” exposure concentrations and conditions and are used as a component of the respirator selection criteria first developed in the mid-1970s [NIOSH 1994]. Since the development of the original IDLH values in the 1970s and their subsequent revision in 1994, NIOSH has continued to review relevant scientific data and conduct research on methods for developing acute inhalation reference values. This document reflects continuing enhancements in risk assessment approaches and provides a detailed description of the current methods used to derive IDLH values. The documentation for specific IDLH values is available as separate NIOSH publications and on the NIOSH website.

The primary objectives of this *Current Intelligence Bulletin* (CIB) are:

1. To provide a brief history of the development of IDLH values,
2. To update the scientific bases and risk assessment methodology used to derive health-based IDLH values based on quality toxicity and human health effects data,

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3. To provide transparency behind the rationale and derivation process for IDLH values, and
4. To demonstrate how scientifically credible IDLH values can be derived based on available data resources.

1.1 Background

The concept of using respirators to protect workers in situations that are immediately dangerous to life or health was discussed at least as early as the 1940's. The following is from a 1944 U.S. Department of Labor (DOL) bulletin:

> - The situations for which respiratory protection is required may be designated as, (1) nonemergency and (2) emergency. Nonemergency situations are the more or less normal ones that involve exposure to atmospheres that are not immediately dangerous to health and life, but will produce marked discomfort, sickness, permanent harm, or death after a prolonged exposure or with repeated exposure. Emergency situations are those that involve actual or potential exposure to atmospheres that are immediately harmful and dangerous to health or life after comparatively short exposures. [Yant 1944]

The Occupational Safety and Health Administration (OSHA) defines an IDLH concentration in the hazardous waste operations and emergency response regulation as follows:

> - An atmospheric concentration of any toxic, corrosive or asphyxiant substance that poses an immediate threat to life or would interfere with an individual's ability to escape from a dangerous atmosphere [29 CFR 1910.120]

In the OSHA regulation on “permit-required for confined spaces,” an IDLH condition is defined as follows:

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- Any condition that poses an immediate or delayed threat to life or that would cause irreversible adverse health effects or that would interfere with an individual's ability to escape unaided from a permit space [29 CFR 1910.146]. Note: Some materials (e.g., hydrogen fluoride gas and cadmium vapor) may produce immediate transient effects that, even if severe, may pass without medical attention, but are followed by sudden, possibly fatal collapse 12-72 hours after exposure. The victim "feels normal" from recovery from transient effects until collapse. Such materials in hazardous quantities are considered to be "immediately dangerous to life or health." [29 CFR 1910.146]

In the current respiratory protection standard, OSHA states that an IDLH condition is as follows:

- An atmosphere that poses an immediate threat to life, would cause irreversible adverse health effects, or would impair an individual's ability to escape from a dangerous atmosphere [29 CFR 1910.134].

As part of this standard, additional guidance is provided by OSHA that dictates the type and application of respirators within IDLH conditions. Specific information that is provided within the respiratory protection standard requires:

- A trained standby person be present with suitable rescue equipment when self-contained breathing apparatus or hose masks with blowers are used in IDLH atmospheres; and
- Persons using air-line respirators in IDLH atmospheres must be equipped with safety harnesses and safety lines for lifting or removing workers from hazardous atmospheres.

The Mine Safety and Health Administration (MSHA) defines IDLH in the program policy manual [56/57.5005(c)] as: The definition of “immediately harmful to life” in this standard is the

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same as that of "immediately dangerous to life or health (IDLH)" as defined by NIOSH, which is "acute respiratory exposure that poses an immediate threat of loss of life, immediate or delayed irreversible adverse health effects, or acute eye exposure that would prevent escape from a hazardous atmosphere."

1.2 The Standards Completion Program

In 1974, NIOSH and OSHA jointly initiated the development of occupational health standards consistent with Section 6(b) of the Occupational Safety and Health Act of 1970 for substances with then-existing OSHA permissible exposure limits (PELs). This joint effort was called the Standards Completion Program (SCP) and resulted in the development of 387 substance-specific draft standards with supporting documentation that contained technical information and recommendations needed for the promulgation of new occupational health regulations. Although new standards were not promulgated at that time, these data became the original basis for the NIOSH/OSHA Occupational Health Guidelines for Chemical Hazards [NIOSH/OSHA 1981].

As part of the respirator selection process for each draft technical standard, an IDLH value was determined for each chemical. The definition used for IDLH values that was derived during the SCP was based on the definition stipulated in 30 CFR 11.3(t). The purpose of deriving an IDLH value was to provide guidance on respirator selection and to establish a maximum exposure concentration in which workers, in the event of respiratory protection failure (e.g., contaminant breakthrough in a cartridge respirator or stoppage of air flow in a supplied-air respirator), could escape safely when the exposure was below the IDLH value. In determining IDLH values, the ability of a worker to escape without loss of life or irreversible health effects was considered along with severe eye or respiratory tract irritation and other deleterious effects (e.g., disorientation or incoordination) that could prevent escape. Although in most cases, egress from a particular worksite could occur in much less than 30 minutes, as a safety margin, IDLH values were based on the effects that might occur as a consequence of a 30-minute exposure. However, the 30-minute period was NOT meant to imply that workers should stay in the work environment

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any longer than necessary following the failure of respiratory protection equipment; in fact, **EVERY EFFORT SHOULD BE MADE TO EXIT IMMEDIATELY!**

1.3 Basis of the Original IDLH Values

IDLH values were determined for each substance during the SCP on a case-by-case basis, taking into account the toxicity data available at the time. Whenever possible, IDLH values were determined using health effects data from studies of humans exposed for short durations. However, in most instances, a lack of human data necessitated the use of animal toxicity data. When inhalation studies of animals exposed for short durations (i.e., 0.5 to 4 hours) were the only health effects data available, IDLH values were based on the lowest exposure causing death or irreversible health effects in any species. When lethal dose (LD) data from animals were used, IDLH values were estimated on the basis of an equivalent exposure to a 70-kilogram (kg) worker breathing 10 cubic meters (m^3) of air. Since chronic exposure data may have little relevance to acute effects, these types of data were used in determining IDLH values only when no acute toxicity data were available and only in conjunction with competent scientific judgment. In a number of instances when no relevant human or animal toxicity data were available, IDLH values were based on analogies with other substances with similar toxic effects.

The basis for each of the 387 original IDLH values determined during the SCP were reviewed and paraphrased from the individual draft technical standards for the publication of the original list of IDLH values. Also included is a complete listing of references cited in the SCP; in many cases where only secondary references were cited, the original sources have also been added. Whenever available, the references (secondary and primary) were obtained to verify the information cited in the SCP. However, a few of the original references, such as personal communications and foreign reports, could not be located.

Although 387 substances were originally included in the SCP, IDLH values were not determined for all of them. The published data at that time for 40 of these substances [e.g., DDT (CAS# 50-29-3) and triphenyl phosphate (CAS# 115-86-6)] showed no evidence that an acute exposure to

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high concentrations would impede escape or cause any irreversible health effects following a 30-minute exposure, and the designation "NO EVIDENCE" was used in the listing of IDLH values. For all of these substances, respirators were selected on the basis of assigned protection factors. For some (e.g., copper fume and tetryl), an assigned protection factor of 2,000 times the PEL was used to determine the concentration above which only the "most protective" respirators were permitted. However, for most particulate substances for which evidence for establishing an IDLH value did not exist [e.g., ferbam (CAS# 14484-64-1) and oil mist (CAS# 8012-95-1)], the use of an assigned protection factor of 2,000 would have resulted in the assignment of respirators at concentrations that were not likely to be encountered in the occupational environment. In addition, exposure concentrations greater than 500 times the PEL for many airborne particulates could result in exposures that would hamper vision. Therefore, it was decided as part of the SCP (and during the review and revision of the IDLH values) that for such particulate substances, only the "most protective" respirators would be permitted for use in concentrations exceeding 500 times the PEL.

IDLH values could not be determined during the SCP for 22 substances [e.g., bromoform (CAS# 75-25-2) and calcium oxide (CAS# 1305-78-8)] because of a lack of relevant toxicity data and therefore, the designation "UNKNOWN" was used in the IDLH value listing. For most of these substances, the concentrations above which only the "most protective" respirators were allowed were based on assigned protection factors that ranged from 10 to 2,000 times the PEL, depending on the substance. There were also 10 substances [e.g., n-pentane (CAS# 109-66-0) and ethyl ether (CAS# 60-29-7)] for which it was determined only that the IDLH values were in excess of the lower explosive limits (LELs). Therefore, the LEL was selected as the IDLH value with the designation "LEL" added in the IDLH value listing. For these substances, only the "most protective" respirators were permitted above the LEL in the SCP draft technical standards.

For 14 substances [e.g., beryllium (CAS# 7440-41-7) and endrin (CAS# 72-20-8)], the IDLH values determined during the SCP were greater than the concentrations permitted based on assigned respiratory protection factors. In most instances the IDLH values for these substances were set at concentrations 2,000 times the PEL.

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1.4 Update of the IDLH Values in 1994

The current NIOSH definition for an IDLH condition, as given in the *NIOSH Respirator Decision Logic* [NIOSH 2004], is a situation "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." It is also stated that the purpose of establishing an IDLH value is to "ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment." The respirator decision logic uses an IDLH value as one of several respirator selection criteria. "Highly reliable" respirators (i.e., the most protective respirators) would be selected for emergency situations, fire fighting, exposure to carcinogens, entry into oxygen-deficient atmospheres, entry into atmospheres that contain a substance at a concentration greater than 2,000 times the NIOSH recommended exposure limit (REL) or OSHA PEL, and for entry into IDLH conditions. These "highly reliable" respirators include either a self-contained breathing apparatus (SCBA) that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode, or a supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary SCBA operated in a pressure-demand or other positive-pressure mode.

When the IDLH values were developed in the mid-1970s, only limited toxicological data were available for many of the substances. In 1993, NIOSH requested information on the uses of IDLH values in the workplace and on the scientific adequacy of the criteria and procedures originally used for establishing them [Federal Register, Volume 58, Number 229, p. 63379, Wednesday, December 1, 1993]. The information received in response to the Federal Register announcement was evaluated and used to establish future actions concerning IDLH values.

While new methodology research efforts were planned and initiated, NIOSH also decided to review the original IDLH values, and revise them as appropriate [NIOSH 1994]. The update was completed in 1994. The 1994 update also included revisions or derivation of IDLH values for 85 substances [e.g., benzene (CAS# 71-43-2) and methylene chloride (CAS# 75-09-2)] determined

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by NIOSH to meet the OSHA definition of "potential occupational carcinogen" as given in 29 CFR 1990.103. For all of these substances, except ethylene oxide (CAS #75-21-8) and crystalline silica (CAS # 14808-60-7), NIOSH recommends that the "most protective" respirators be worn by workers exposed at concentrations above the NIOSH REL, or at any detectable concentration when there is no REL. For ethylene oxide and crystalline silica, NIOSH recommends that the "most protective" respirators be worn in concentrations exceeding 5 parts per million (ppm) and milligrams per cubic meter of air (mg/m^3), respectively [NIOSH 1989, 2004].

1.5 Purpose and Objectives of the IDLH Values

IDLH values have traditionally been identified as a key component of the decision logic for the selection of respiratory protection devices. For example, the NIOSH *Respirator Selection Logic* [NIOSH 2004] states that the purpose of establishing an IDLH value is (1) to ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment and (2) is considered a maximum level above which only a highly reliable breathing apparatus providing maximum worker protection is permitted. Since the inception of IDLH values as part of the SCP, occupational health professionals have employed these values beyond their initial purpose as a component of the NIOSH *Respirator Selection Logic*. Examples of such applications of the IDLH values include the development of Risk Management Plans (RMPs) for non-routine work practices governing operations in “high” risk environments (e.g., confined spaces) and the development of Emergency Preparedness Plans (EPPs), which provide guidance for emergency response personnel and workers during unplanned exposure events. This CIB presents a protocol for the derivation of health-based IDLH values capable of being used within both the traditional role of respirator selection and in the non-traditional applications including the development of RMPs and EPPs.

The scientific rationale and derivation process outlined in this CIB has been established to ensure that a consistent approach is used for development of health-based (i.e., toxicity-based) IDLH

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values. According to this protocol, IDLH values are based on health effects considerations determined through a critical assessment of the toxicology and human health effects data. This approach ensures that the IDLH values reflect an airborne concentration of a substance that represents a "high risk" situation that may endanger workers' life or health. The emphasis on health effects is consistent with both the traditional use of IDLH values as a component of the respirator selection logic and the growing applications of IDLH values in guiding accident prevention and emergency response planning. It is important to note that IDLH values are concentrations that may cause adverse effects, and thus, they are not intended to be used as surrogates for occupational exposure limits (OELs). OELs, such as NIOSH RELs, are intended to protect workers from adverse health effects associated with repeated chemical exposure for 10-hour shifts during a 40-hour work week for a working lifetime. The IDLH values should not be used as comparative indices of toxicity or to infer a "safe" level for exposures to chemicals under routine occupational exposure conditions (see *Section 2.3*). A situation resulting in airborne concentrations at or near the IDLH value should be considered a once-in-a-lifetime event and exposure duration should not exceed 30 minutes. All available precautions should be taken to ensure that workers exit the environment immediately if exposures are at or near concentrations equivalent to IDLH values.

NIOSH recognizes that in some cases a health-based IDLH value might not account for all workplace hazards, such as safety concerns and considerations. Situations and conditions that might preclude the use of a health-based IDLH value include, but are not limited to:

- Where the IDLH value based on health effects considerations is above the concentration that would result in oxygen deprivation (oxygen concentration of less than 19.5%). Chemicals capable of causing such conditions include inert gases such as argon (CAS# 7440–37–1), carbon dioxide (CAS# 124-38-9) and nitrogen (CAS# 7727-37-9)].
- Where the IDLH value based on health effects considerations is higher than a particulate concentration that generates significant hazards from reduced visibility. Such conditions may occur within processes that generate dust plumes

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in enclosed areas or confined spaces (e.g., grinding, milling, or mining operations) and structural fires.

- Where the IDLH value based on health-effects considerations is greater than 10% of the lower explosive limit (LEL) concentration or the minimum concentration of gas or vapor in air below which propagation of a flame does not occur in the presence of an ignition source. Chemicals capable of causing such conditions include flammable gases or vapors such as acetone (CAS# 67-64-1), ethyl acetate (CAS# 64-17-5) and n-pentane (CAS #109-66-0).
- Where the IDLH value based on health effects considerations is greater than the time-weighted average (TWA) occupational exposure limit (OEL) multiplied by the assigned protection factor for the most protective respirator. Since IDLH values are based on acute exposure and health effects data, the most protective respirator may not be adequately protective for full-shift exposures at this concentration. Examples of substances where this situation may occur include chromic acid and chromates (CAS# 1333–82–0), lead compounds (CAS# 7439–92–1, metal).

In such cases, it is important that safety hazards or other considerations be taken into account. Information on the non-health based hazards will be incorporated within the support documentation (see *Appendix A*) for an IDLH value to aid occupational health professionals in the development of RMPs for non-routine work practices governing operations in "high" risk environments (e.g., confined spaces) and EPP. For example, in the event that the derived health-based IDLH value exceeds 10% of the LEL concentration for a flammable gas or vapor the following hazard statement will be included within the support documentation: "The health-based IDLH value is greater than 10% of the LEL (>10% LEL) of the chemical of interest in air. Therefore, safety considerations against hazard of explosion must be taken into account." In addition, the notation (> 10 % LEL) will appear beside the IDLH value within the *NIOSH Pocket Guide to Chemical Hazards* [NIOSH 2005] and other NIOSH publications. Similar statements will be developed as needed for other non-health based hazards and considerations. The use of

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hazard statements and notations to provide supplemental information on non-health based hazards and considerations aligns with the protocols used to derive the Acute Exposure Guideline Levels (AEGLs) by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) [NAS 2001].

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Chapter 2.0-Comparison of IDLH Values to Alternative Short-term Exposure Limits/Values

An important step in the development of IDLH values is the review of alternative short-term exposure limits/values developed by other agencies and organizations. The review of such information serves several purposes, including:

- Review of alternative short-term exposure limits/values is useful for verifying that all key data and scientific issues are considered and thus serves as one step in verifying that a robust literature search has been completed.
- Review of assessments by other agencies and organizations assists in identifying critical issues with study design, methodology, or results for critical studies that must be considered in developing an IDLH value.
- In some cases, alternative exposure limits/values may aid in determining a potential range for the IDLH value (after taking into account the methodology differences used to develop various short-term limits/values) as described later in this section.

Because the documentation for the IDLH values is intended to be a concise summary document, NIOSH incorporates in the IDLH documentation information on the acute effects of chemicals and selected short-term limits/values from other in-depth peer-reviewed assessments for comparison purposes. Table 2.1 summarizes several of the short-term exposure limits/values most commonly evaluated during the derivation of IDLH values. There are other numerous sources of short-term exposure limits/values that may be reviewed on a case-by-case basis for a particular chemical depending on availability.

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Table 2.1: Short-Term Exposure Limits/Values by other Agencies and Organizations

Purpose of Short-term Exposure Limit	Agency or Organization Designation
Acute exposure guidelines for protection of the general public during emergency or unusual releases.	Acute Exposure Guidelines Levels (AEGLs) Emergency Response Planning Guidelines (ERPGs) Other values as appropriate
Acute exposure guidelines for potential routine acute exposures in the workplace such as short term exposure limits (STEL) or Ceiling Limits ("C").	NIOSH RELs OSHA PELs American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs)® American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Levels (WEELs) Other values as appropriate

Although IDLH values may rely on much of the same acute health effects information used to derive alternative short-term exposure limits/values, there are underlying differences in the intended use of the various acute exposure values. Therefore, review of documentation for these alternative short-term limits/values provides information to guide IDLH value development, but the actual proposed values are not directly comparable. The remaining sections of Chapter 2.0 discuss the different purposes and populations protected by commonly reviewed alternative short-term exposure limits/values.

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2.1 Acute Exposure Guideline Levels (AEGLs)

AEGLs represent threshold exposure limits for emergency exposures that are used for a variety of applications in planning, response and prevention in the community, the workplace, transportation, the military and the remediation of Superfund sites. Three levels, referred to as AEGL-1, AEGL-2 and AEGL-3, are developed for each of five exposure periods (10 minutes , 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows [NAS 2001]:

- AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
- AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
- AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing irritation or asymptomatic, non-sensory effects, such as non-disabling odor and taste. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or

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idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

Like the IDLH value, the AEGL-2 is designed to protect from irreversible or other serious effects and escape-impairing effects. Thus, the effects that are the basis for the AEGL-2 closely match those of interest for the IDLH value. In addition, the AEGLs include a 30-minute value, which is the same duration of interest for the IDLH values. One significant difference between the IDLH value and that of the AEGL-2 is that the AEGL-2 is designed to protect the general population, including potentially-sensitive subpopulations (i.e., children, elderly, and individuals with pre-existing health impairments), while the IDLH value is designed for worker populations, which are assumed to be less sensitive on average than the general population. This assumption is based on the consideration that there would be a smaller likelihood for significant inclusion of specific sensitive subpopulations in the population of working adults. This means that given the same set of data, the IDLH value will often be in the range of the 30-minute AEGL-2, but somewhat above it since the additional consideration of sensitive subpopulations is not as significant a consideration for occupational exposures designed to protect generally healthy worker populations. The IDLH value is usually below the 30-minute AEGL-3, since, for most chemicals, serious or escape-impairing effects relevant for IDLH values occur at concentrations below the lethality threshold. In light of these considerations, recent AEGL-2 and AEGL-3 values can provide a rough gauge for identifying a potential range for the IDLH value. Exceptions may occur, partially because the AEGL process follows fairly strict methodology guidelines [NAS 2001], including the use of default approaches in the absence of chemical specific data, while the process for developing IDLH values relies heavily on the overall weight of evidence with limited use of default procedures. The extensive AEGL documentation for each chemical has been thoroughly reviewed by expert committees and is often a useful resource for de novo analyses. In addition, the AEGL documentation includes detailed analysis of all key studies, often including calculation of the value of the ten Berge exponent “n” [ten Berge et al. 1986]; for a detailed description of the ten Berge exponent see *Section 3.5 – Time Scaling*.

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The AEGL values are derived by the NAC/AEGL Committee, which is a Federal Advisory Committee Act (FACA) committee established to identify, review and interpret relevant toxicologic and other scientific data and to develop AEGLs for high priority, acutely toxic chemicals (available online at: http://www.epa.gov/oppt/aegl/). The NAC/AEGL Committee includes members from federal and international agencies [e.g., NIOSH, U.S. Environmental Protection Agency (USEPA), U.S. Department of Transportation (DOT), U.S. Department of Defense (DOD), U.S. Department of Energy (DOE), Agency for Toxic Substances and Disease Registry (ATSDR), Canadian Government, Netherlands National Institute for Public Health and the Environment (RIVM)], state agencies and environmental organizations, academia, private industry, international and nonprofit organizations]. Interim AEGLs prepared by the AEGL committee, after stakeholder comment, are reviewed by the National Academy of Sciences (NAS)/National Research Council (NRC) AEGL subcommittee before finalization.

2.2 Emergency Response Planning Guidelines (ERPGs)

ERPGs are developed by the AIHA for emergency planning and are intended as health-based guideline concentrations for single exposures to chemicals. These guidelines (i.e., the ERPG Documents and ERPG values) are intended for use as planning tools for assessing the adequacy of accident prevention and emergency response plans, including transportation emergency planning and for developing community emergency response plans.

As with AEGLs, there are three ERPG guidance concentration levels designed for community protection [AIHA 2009]. However, ERPGs are derived for only single exposure durations of 1 hour. Each of the three levels is defined and briefly discussed below:

- ERPG-1: The maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

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The ERPG-1 identifies a level which does not pose a health risk to the community but which may be noticeable due to slight odor or mild irritation. In the event that a small non-threatening release has occurred, the community could be notified that they may notice an odor or slight irritation but that concentrations are below those which could cause unacceptable health effects. For some materials, because of their properties, there may not be an ERPG-1. Such cases would include substances for which sensory perception levels are higher than the ERPG-2 level. In those cases, the ERPG-1 level would be given as "Not Appropriate." It is also possible that no valid sensory perception data are available for the chemical. In these cases, the ERPG-1 level would be given as "Insufficient Data."

- ERPG-2: The maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms which could impair an individual's ability to take protective action.

- Above ERPG-2, there may be significant adverse health effects, signs, or symptoms for some members of the community which could impair an individual's ability to take protective action. These effects might include severe eye or respiratory irritation, muscular weakness, central nervous system (CNS) impairments, or serious adverse health effects.

- ERPG-3: The maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

The ERPG-3 level is a worst-case planning level above which there is the possibility that some members of the community may develop life threatening health effects.

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> This guidance level could be used to determine the airborne concentration of a chemical that could pose life threatening consequences should an accident occur. This concentration could be used in planning stages to project possible levels in the community. Once the distance from the release to the ERPG-3 level is known, the steps to mitigate the potential for such a release can be established.

Like the IDLH value, the ERPG-2 is designed to protect from irreversible or other serious and escape-impairing effects, and so is based on similar effects as those considered as the basis for IDLH values. Like the IDLH values, ERPGs are for acute exposure, but they are based on a 1-hour exposure, rather than 30 minute exposures. All other things being equal, this would mean that ERPG-2 values will generally be lower than the corresponding IDLH value, since the potential exposure time for the ERPG is higher. Moreover, even though ERPGs are developed by an occupational health organization, ERPGs are more like the AEGLs, in that they are designed to protect the general population, and thus susceptible populations are more of a consideration for ERPGs than for IDLH values.

2.3 Occupational Exposure Limits

OELs are derived by various governmental, nongovernmental, and private organizations for application to repeated or daily worker exposure situations. For example, in the United States, OELs are developed by several organizations. Examples of such organizations and their respective OEL values include; NIOSH RELs, OSHA PELs, MSHA RELs, ACGIH TLVs®, and AIHA WEELs. While the exact definition varies among organizations (see *Glossary*), the general intent of OELs is to identify airborne concentrations of substances in the air to which all or nearly all workers can be exposed on a repeated basis for a working lifetime without adverse health effects. OELs are developed based on available human data, such as results from epidemiologic studies or controlled human exposure studies, from animal toxicology studies, or a combination of human and animal data. The health basis on which exposure limits are established may differ from substance to substance; protection against impairment of health may

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be a guiding factor for some, whereas reasonable freedom from irritation, narcosis, nuisance, or other forms of stress may form the basis for others. For most OELs, health impairment refers to effects that shorten life expectancy, compromise physiological function, impair the capability for resisting other toxic substances or disease processes, or adversely affect reproductive function or developmental processes.

OELs are guidelines (or, laws if mandated by OSHA and MSHA) intended for use in the practice of industrial hygiene, for the control of potential workplace hazards. OELs are not intended for use in other situations, such as the evaluation or control of ambient air pollution, or for estimating the toxic potential of continuous uninterrupted exposures or other exposure scenarios involving extended work periods, or as proof of existing disease or physical conditions. OELs do not clearly delineate between safe and dangerous concentrations, nor are they a relative index of toxicity.

There are three primary categories of OELs, each with a different exposure duration comparison. The first category defines the TWA exposure concentration for up to a 10-hour workday (NIOSH REL) or a conventional 8-hour workday (OSHA PEL, MSHA PEL, ACGIH TLV® or AIHA WEEL) during a 40-hour work week, to which it is believed that all (for the REL and PEL) or nearly all workers (for the TLV®) or most workers (WEEL) may be repeatedly exposed daily without adverse effects. The second category of OEL, called short-term exposure limit (STEL) and is designated by ST preceding the value for NIOSH RELs, is a 15-minute TWA that should not be exceeded at any time during a work day. ACGIH describes the TLV-STEL as the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from irritation, chronic or irreversible tissue damage, or narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue, or materially reduce work efficiency [ACGIH, 2009]. Exposures above the TLV-TWA and up to the TLV-STEL should not be longer than 15 minutes and should not occur more than four times per day with a minimum of 60 minutes between exposures in this range [ACGIH, 2009]. The last category of OELs, referred to as ceiling OEL and designated by ACGIH with a “C” preceding

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the value, is the concentration that should not be exceeded during any part of the working exposure, unless otherwise noted [ACGIH 2009].

Like the IDLH values, OELs are aimed at worker populations, and so consideration of susceptible populations is of less significance than for general population values. STELs and ceiling OELs are acute exposure values, while the TWA OELs are for repeated, chronic exposure. STELs are for a shorter duration (15 minutes), compared to 30 minute IDLH values, and repeated exposures are permitted during the work shift at this airborne concentration. STELs can be based on some endpoints similar to those that are of concern for the IDLH value (e.g., chronic or irreversible tissue damage, narcosis that would impair self-rescue). For other endpoints, the severity for the basis of STELs may be less severe than that for the IDLH value. For example, mild irritation that would not be escape-impairing and mild narcosis that affects work efficiency but is not escape-impairing, could be the basis for a STEL, but would be considered below the threshold of interest for an IDLH value. Thus, depending on the nature of the effect caused by the chemical, the IDLH value may or may not be comparable to a STEL value for the same substance.

2.4 Other Acute Inhalation Exposure Limits/Values

A number of other governmental agencies and organizations also develop, or have developed, acute inhalation exposure limits/values intended to address various applications, exposed populations and durations. These include acute exposure limits/values for the general population, as listed in Table 2.4.1.

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Table 2.4.1: Other Sources of Acute Inhalation Exposure Limits/Values

Governmental Agencies and Organizations	Acute Inhalation Exposure Limits/Values	Source
Department of Energy (DOE)	Temporary Emergency Exposure Limits (TEELs)	Craig et al. [2000]; US DOE [2008]
State Agencies (California, Texas, Minnesota, New York, New Jersey, etc.)	State Exposure Limits	MDH [2010]; TCEQ [2010] Cal/EPA [2010]; NJ RTK [2010]
National Academy of Science/ National Research Council (NAS/NRC)	Emergency and Continuous Exposure Guidance Levels (EEGLs)	NAS [1986]
National Academy of Science/ National Research Council (NAS/NRC)	Short-term Public Emergency Guidance Levels (SPEGLs)	NAS [1986]
NAS/NRC	Spacecraft Maximum Allowable Concentration (SMAC)	NASA [1999]
U.S. Environmental Protection Agency (USEPA)	Acute reference concentrations (RfCs)	USEPA [2009]
USEPA's homeland security program (DHS)	Provisional Advisory Levels (PALs) for Hazardous Agents	US DHS [2009]

Documentation for acute exposure limits/values from these selected organizations are reviewed and considered if they are deemed to provide specific insights that impact the development or interpretation of the IDLH value. For example, acute exposure limits/values from other government agencies and organizations might be included in the documentation for IDLH values if they are more recent or have unique data not available in other sources.

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Chapter 3.0- Criteria for Determining IDLH Values

A weight-of-evidence approach based on scientific judgment is used in developing the IDLH values, both for evaluating the quality and consistency of the scientific data, and in extrapolating from the available data to the IDLH value. The weight-of-evidence approach refers to the critical examination of all the available data from diverse lines of evidence and deriving a scientific interpretation based on the collective body of data, including its relevance, quality, and reported results. This is in contrast to a purely hierarchical or strength-of-evidence approach that would use rigid decision criteria for selecting a critical adverse effect concentration and applying default UF to derive the IDLH value. The documentation of the IDLH value for each chemical is not intended to be a comprehensive review of all the available studies; instead, it focuses on the key data, decisions points and scientific rationale integrated into the overall weight of evidence applied to derive the IDLH value for a chemical of interest. An example of the documentation for development of an IDLH value is provided in Appendix A that explains the logic and rationale behind the derivation of the IDLH values for vinyl acetate (CAS# 108-05-4).

Because IDLH values are often developed from limited data, the process for developing a value often applies data from multiple lines of evidence, rather than a single key high quality study. Overall, the following approach is used for deriving IDLH values:

- Critical review of human and animal toxicity data to identify potential relevant studies and characterize the various lines of evidence that can support the derivation of the IDLH value;
- Application of duration adjustments to determine 30-minute equivalent exposure concentrations, and conduct of other dosimetry adjustments as needed;
- Application of an uncertainty factor (UF) for each potential point of departure (POD) or critical adverse effect concentration identified from the available studies to account for issues associated with inter- and intraspecies differences, the severity of the observed effects (including concern about cancer or reproductive or developmental toxicity), data quality or data insufficiencies; and

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- Developing the final recommendation for the IDLH value from the various alternative lines of evidence using a weight of evidence approach from all of the data.

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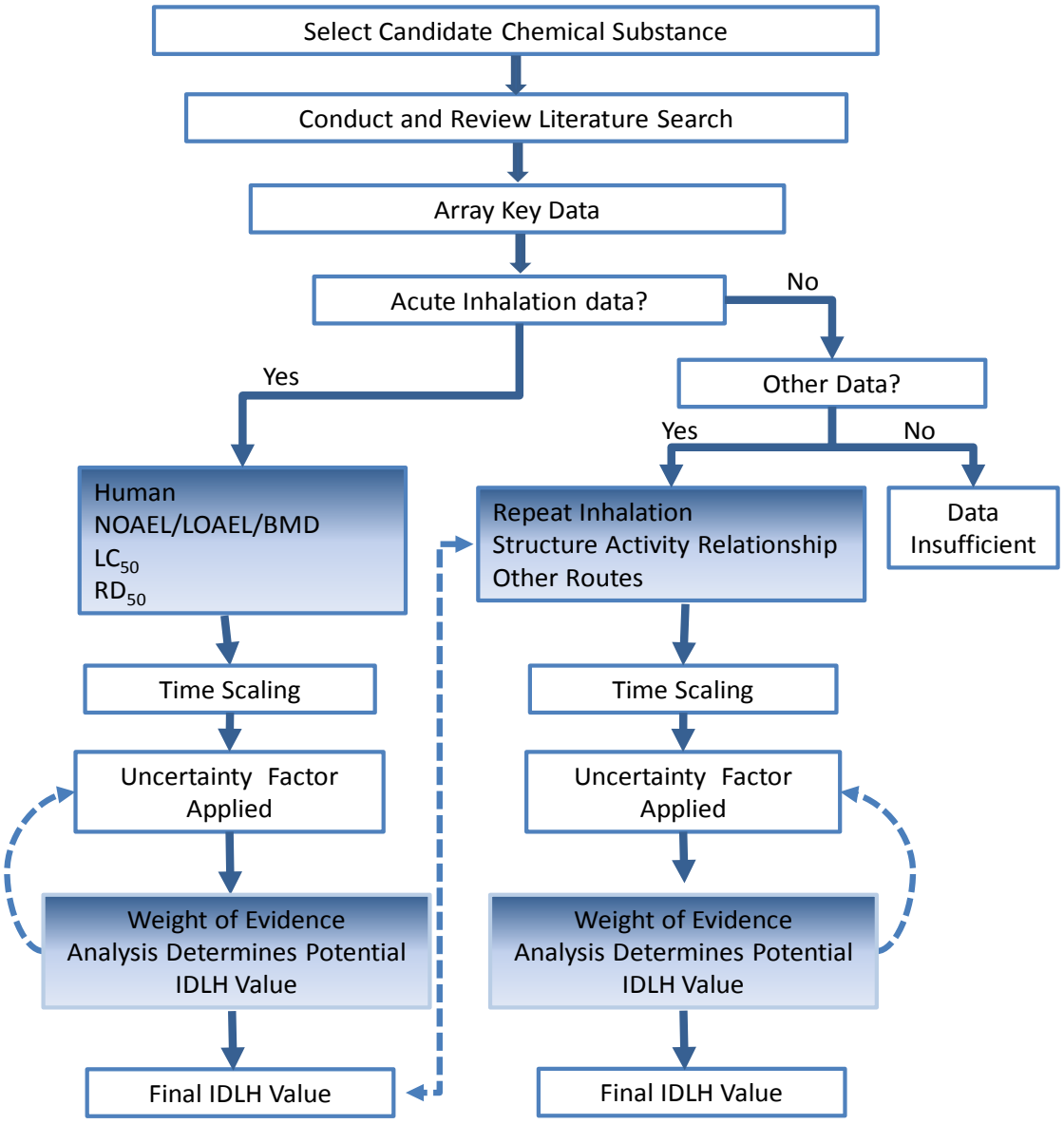
Figure 3.0 provides a detailed summary of the view of key steps of the derivation of IDLH values.



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This process (see *Figure 3.0*) is conceptually similar to that used in other risk assessment applications, including the process steps of:

- Hazard characterization,
- Identification of critical effects,
- Identification of a POD,
- Application of appropriate UF based on the study and POD, and
- Determination of the final risk value.

However, rather than narrowing the analysis to a single study because of the limited data available on many substances, the weight-of-evidence approach, which is more integrative, is used to develop the IDLH value based on consideration of alternatives and different lines of evidence. In particular, application of the appropriate UF to each potential POD allows for consideration of the impact of the overall dataset as well as the uncertainties associated with each potential key study in determining the final IDLH value. See Appendix A for an example of how a typical dataset is evaluated to derive an IDLH value.

As illustrated in the remainder of this CIB, derivation of IDLH values uses a systematic data evaluation process that gives preference for data that provides the greatest degree of confidence in the assessment. The approach describes some overall preferences that define a general data hierarchy, but the methodology allows for all of the data to be evaluated using a weight-of-evidence approach to develop a toxicologically-meaningful IDLH value that is consistent with the dataset as a whole. Implementing such a procedure requires considerable expertise and relies heavily on weighing various lines of evidence with vetting by multiple scientists through a rigorous peer review processes. Thus, while the following sections describe general processes and priorities for use of the data, these approaches are provided as general guidance, and the focus is on interpretation of the overall database.

3.1 Importance of Mode of Action and Weight of Evidence

The mode of action (MOA), meaning a general description of how a chemical exerts its toxic effects, is an important part of the evaluation of chemical data and development of IDLH values.

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MOA can be thought of as a general category of how a chemical acts to cause adverse effects. Note that the MOA is a general description of the biological basis for toxicity, and does not require the detailed level of understanding implied by mechanism of action. The MOA for a chemical is identified based on the observed toxic effects, any mechanistic data, structure-activity data and information on related chemicals; many chemicals act by more than one MOA. For example, many solvents cause both respiratory irritation and CNS effects. Some of the more common classes of MOA that are encountered in developing IDLH values, and examples of chemicals that fall into these classes, include:

- Direct Irritants: Chemicals with this MOA are often highly reactive and/or corrosive, including acids, bases and halogen gases. Endpoints commonly reported include eye, nose, and throat irritation, with higher concentrations typically leading to irritation and tissue damage lower in the respiratory tract. Chemicals in this class include organic solvents, [e.g., vinyl acetate (CAS# 108-05-4)], organic acids, [e.g., acrylic acid (CAS# 79-10-7)]; halogens and other reactive gases [e.g., bromine (CAS# 7726-95-6)]; and some metal compounds, [e.g., titanium tetrachloride (CAS# 7550-45-0)]. Sensory irritants, [e.g., chloropicrin (CAS# 76-06-2)], cause the sensation of irritation at concentrations much lower than those causing tissue damage, while irritation from reactive gases is the result of the tissue damage.
- Nervous System Effects: Chemicals can cause nervous system effects by different MOAs. Many solvents, [e.g., chloroform (CAS# 67-66-3) and 1,1,1-trichloroethane (CAS# 71-55-6)], as well as other chemicals, cause CNS depression. Clinical signs reported in humans may include fatigue, weakness and headaches. Endpoints commonly reported in animals or humans include sedation and reduced performance in specialized neurological testing. Certain classes of pesticides (e.g., organophosphates and carbamates) and nerve agents [e.g., sarin (CAS# 107-44-8)] inhibit the action of the enzyme acetylcholinesterase. Early signs of exposures to such agents include miosis (constriction of the eye pupil), excessive salivation, and muscle twitching.

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- Metabolic Toxicants: This class of chemicals acts by interfering with the cell's ability to generate and store energy and includes chemicals, (e.g., cyanides and azides). Initial effects of these chemicals are on the CNS, with some symptoms similar to those noted above for CNS depressants and toxicity ultimately leading to respiratory failure.
- General Systemic Target Organ Toxicants: High-level exposures to some chemicals can result in toxicity to such organs as the liver or kidney. Such endpoints are typically not monitored in acute lethality studies, but an in-depth study of a single inhalation exposure may include evaluation of histopathology or clinical chemistry, and acute poisoning incidents in humans may indicate that the liver or kidney is a target. The liver and kidney are frequently the most sensitive systemic targets, due to the high blood flow to these organs and their capacity for metabolizing chemicals to more reactive forms.
- Special Target Organ Effects: Some chemicals target specific organs other than the liver or kidney. For example, arsine (CAS# 7784-42-1) causes hemolysis (breakage of red blood cells), with accompanying symptoms of headache, nausea and shortness of breath. A number of halogenated hydrocarbons, [e.g., vinyl chloride (CAS# 75-01-4), HFC-134a (CAS# 811-87-2) and HCFC-141b (CAS# 1717-00-6)], cause cardiac sensitization. Hormonally-mediated effects can be suggested by direct observations of effects on reproductive function or toxicity studies evaluating fetal development. For example, hexafluoroacetone (CAS# 684-16-2) and 1-bromopropane (CAS# 106-94-5) cause reproductive toxicity.
- Asphyxiants: Inert gases, [e.g., nitrogen (CAS# 7727-37-9) and argon (CAS# 7440–37–1)], cause health effects by displacing oxygen. Chemical asphyxiants, [e.g., carbon monoxide (CAS# 630-08-0), hydrogen cyanide (HCN; CAS# 74-90-8) and hydrogen sulfide (CAS# 7783-06-4)], can interfere with the body's ability to use oxygen. Some early symptoms of asphyxiation include headache, rapid breathing, heart palpitations and lethargy.

MOA is considered as part of the evaluation of need for and adequacy of UF in extrapolation from various points of departure. The MOA of a substance is used during the derivation of

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IDLH values to determine UF, time extrapolation, choice of POD and consideration of interspecies differences. Some examples of how MOA affects these considerations include:

- A smaller UF is used when the endpoint is known to be very sensitive (e.g., cardiac sensitization in response to an epinephrine challenge, which is considered a sensitive marker of a severe effect). Similarly, a smaller UF may be used for a sensory irritation endpoint, due to the relatively small variability in the human population for this endpoint.
- MOA information may also be used to support a flatter time extrapolation curve for sensory irritants, based on the observation that effects from such chemicals (after the first few minutes of exposure) are driven primarily by concentration and less by duration of exposure.
- MOA information indicating that the chemical targets the portal of entry, with resulting effects such as eye, nose and throat irritation, would indicate that the route-to-route extrapolation is not appropriate.
- MOA information may suggest the use of surrogates when information on the chemical of interest is limited, such as the use of HCN (CAS# 74-90-8) as a surrogate for acetocyanohydrin (CAS# 78-97-7), which spontaneously dissociates into acetone (CAS# 67-64-1) and HCN.
- Finally, MOA information may suggest potential refinements to the dose-response analysis. For example, carbon monoxide toxicity is due to the formation of carboxyhemoglobin (COHb), and the IDLH value for carbon monoxide is based on calculated COHb levels.

3.2 Process for Prioritization of Chemicals

In addition to serving as a crucial factor in the selection of respiratory protection equipment, IDLH values play an important role in planning work practices surrounding potential emergency high exposure environments in the workplace and in guiding actions by emergency response personnel during unplanned exposure events. Ideally, such guidance values would be available for all chemicals that might be present under high exposure situations. However, the

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development of IDLH values is not necessary for many chemicals, such as those with very low exposure potential or those that do not exhibit significant acute toxicity via the inhalation route. A prioritization process is used by NIOSH to ensure that that resources allocated to IDLH value development yield the greatest impact on risk reduction. This process takes into account both toxicity and exposure potential, and is applied to a broad range of potentially hazardous chemicals (e.g., chemical warfare agents, industrial chemicals or agrochemicals) subject to emergency or uncontrolled releases. A qualitative algorithm is used to generate a priority ranking. This process provides ***initial*** priority rankings based on a simple approach that uses readily available sources of information. More sophisticated hazard or risk-based ranking schemes could be used, but gathering and analyzing the data would require the same approximate effort required to actually derive an IDLH value. A complex ranking approach would not meet the primary objective to quickly and efficiently identify chemicals of greatest concern. The resulting priorities are further modified based on current NIOSH emphasis areas. For example, chemicals can be added or removed from the priority list based on new information related to toxicity or exposure potential. The development and use of a documented prioritization process allows for more frequent updating by NIOSH of both input data and prioritization criteria to meet changing needs. The prioritization approach is described more fully in Appendix B.

3.3 Literature Search Strategy

NIOSH performs in-depth literature searches to ensure that all relevant human and toxicity information associated with acute exposures to the substance are identified. An initial literature search is done, including searches for information from the sources listed in Table 3.3.1.

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Table 3.3.1: Literature Search Sources

DATABASE	LINK
CDC/ATSDR ToxProfiles	http://www.atsdr.cdc.gov/toxpro2.html
CHEMID	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CHEM
EU, European INventory of Existing Commercial chemical Substances (EINECS)	http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ein
EMBASE	http://www.embase.com/
National Library of Medicine (NLM), Haz-Map	http://hazmap.nlm.nih.gov/
NLM, HSDB	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
International Agency for Research on Cancer (IARC)	http://www.iarc.fr/
World Health Organization (WHO)/IPCS International Chemical Safety Card (ICSC)	http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/index.htm
ITER	http://iter.ctcnet.net/publicurl/pub_search_list.cfm
New Jersey Hazardous Substance Fact Sheets (NJ-HSFS)	http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx
NIOSHTIC2	http://www2a.cdc.gov/nioshtic-2/default.asp
OSHREFS	http://elib2.cdc.gov:2357/bibliographic/search.html
NLM, PUBMED	http://www.ncbi.nlm.nih.gov/pubmed/
NIOSH, RTECS	http://www.cdc.gov/niosh/rtecs/
NLM, TOXLINE	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
Web of Science	http://thomsonreuters.com/products_services/science/science_products/scholarly_research_analysis/research_discovery/web_of_science

Electronic searches of these databases are conducted with limitations on search dates. The databases are searched for studies pertinent to acute inhalation toxicity using the following search terms summarized in Table 3.3.2.

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Table 3.3.2: Literature Search Key Words

Search Terms
Acute
Inhalation
Lethal
Lethal Concentration
LC
Fatal
Fatality
Irritation
Respiratory
RD
Threshold
Case Study
Poisoning
Chemical Identifiers

The electronic literature searches are screened for relevant articles and a bibliography of relevant literature is compiled that identifies studies for retrieval and review. Peer-reviewed toxicology reviews are also examined, including those identified by searching the databases and organization websites as noted in Table 3.3.1. Toxicology reviews that are routinely used to identify pertinent literature for developing the IDLH value include those published by AIHA (i.e., ERPG and WEEL documentation), ATSDR (i.e., Toxicology Profiles), National Toxicology Program (NTP), NIOSH (i.e., REL documentation), NRC (i.e., AEGL documentation), OSHA (i.e., PEL documentation), WHO (i.e., Environmental Health Criteria) and USEPA (i.e., IRIS Toxicological Reviews). Other key unpublished literature, such as toxicological reports on file with the USEPA as part of the Toxic Substance Control Act Section 8D, may become available from stakeholders and other interested parties during the external and stakeholder review process.

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3.4 Determining the Critical Study and Endpoint

Development of an IDLH value begins with the critical evaluation and array of the available animal toxicity and human health effects data. In order to effectively evaluate the data, it is useful to array the following information:

- Description of the test species,
- Health endpoints evaluated,
- Exposure concentrations,
- Critical effect levels (e.g., NOAELs, LOAELs, LC_{50} values, etc.), and
- Duration of the exposure for the study.

Once this information is compiled critical effect levels are adjusted to a 30-minute equivalent concentration to derive a POD estimate for each study or study endpoint. Appendix A provides examples of how such information is compiled and used in the derivation of IDLH values for three chemicals. The weight given to each study in selection of a final POD is based on the reliability of the reported findings (as determined from an assessment of study quality), the relevance of the study type for predicting human effects from acute inhalation exposure, and the estimated 30-minute adjusted effect level.

3.4.1 Study Quality Considerations

For toxicology studies, quality considerations that affect the reliability of each study include the key elements of the study design and the adequacy of study documentation. Examples of such aspects of study quality include:

- Relevance of the exposure regimen to a single 30-minute inhalation exposure;
- Quality of atmosphere generation system and analytical techniques used to assess exposure conditions;
- Degree of evaluation of toxic endpoints; and

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- Number of animals used and relevance of the test species to humans.

Other considerations for evaluation of study quality include the reliability of the cited data source, whether the study adhered to or was equivalent to current standards of practice [e.g., USEPA or Organisation for Economic Co-operation and Development (OECD) test guidelines], and whether good laboratory practices (GLPs) were followed. These considerations are evaluated for each study using the general concepts outlined by Klimish et al. [1997]. While a single authoritative guide to such study quality evaluation for epidemiology studies is not available, human effects data studies are judged based on current standards of practice for conducting epidemiology or clinical studies [USEPA 1994; Federal Focus Inc. 1995; Lewandowski and Rhomberg 2005]. Consistency of effects across studies and consistency based on other information available about the chemical (e.g., oral data, structure-activity data) are used to assess the quality of individual studies.

Selection of the critical study to serve as the basis for the IDLH relies heavily on study quality considerations. A high quality study might be chosen as the basis for the IDLH value, even if a lower IDLH value could be generated from a low quality study, where the evaluation of quality casts doubt on the reliability of the study results. An LC_{50} value derived from a USEPA or OECD guideline compliant acute lethality study with robust atmosphere generation and measurement systems may be selected over a lower LC_{50} value from an older study that used a static exposure chamber system and reported only nominal air concentrations or that used a small number of animals or non-standard test species.

3.4.2 Study Relevance Considerations

The weight-of-evidence approach requires a critical evaluation of each study as to its relevance to the ultimate goal of the IDLH value derivation – to develop a scientifically-based estimate of the 30-minute human threshold concentration for severe, irreversible or escape impairing effects. The methodology for developing IDLH values used during the SCP followed a hierarchical approach based on the following preference for data:

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- Acute human inhalation toxicity data,
- Acute animal inhalation toxicity data,
- Acute animal oral toxicity data,
- Data for longer-term inhalation studies, and
- Data for analogous chemicals (i.e., toxicological surrogates).

The updated approach for IDLH value development described in this CIB follows similar principles, but is based more on an overall weight-of-evidence approach that considers study reliability, quality (as discussed in Section 3.4.1), relevance and the magnitude of the observed effect levels. The evaluation of study relevance includes the type and severity of the effects observed, study duration and route of exposure.

3.4.2.1 Relevance of the Type and Severity of the Effect

3.4.2.1.1 General Considerations in Identifying the Severity of Effects for IDLH Derivation

Relevance of the effect is evaluated in the context of the goal for deriving an IDLH value (i.e., to develop a high-confidence estimate of the 30-minute human threshold concentration for severe, irreversible or escape impairing effects). Studies that identify with good precision the actual threshold for such effects are rare, and so usually it is necessary to either extrapolate from an effect level that is above a threshold by relying on a lowest observed adverse effect level (LOAEL) for severe or escape-impairing effects, or to use a lower bound estimate of the threshold by relying on a no observed adverse effect level (NOAEL) for severe or escape-impairing effects. In some cases, concentration modeling can be used to further refine such estimates based on actual study concentrations. All of the data for effects relevant to the IDLH are evaluated and used in this effort, including data on mortality, severe or irreversible effects and escape-impairing effects. Data on exposure levels causing less severe effects, which are below the threshold of interest, are useful as estimates of the NOAEL for severe effects or escape-impairment. Together these data can describe the exposure-response relationship for the chemical of interest, which compares the estimated exposure concentration to the reported

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effects. By understanding this relationship, the potential region of the threshold concentration can be more accurately determined for the most sensitive severe or escape impairing effects.

Table 3.4.2.1 illustrates how the severity of effect is taken into account in determining the POD and IDLH value. In this case, human data are available for a 30-minute exposure that describe the concentration response, from no effects at 10 ppm, to mild irritation at 20 ppm and severe irritation that was considered escape-impairing at 30 ppm. Thus, the threshold for an escape-impairing effect in humans is between 20 and 30 ppm for a 30-minute exposure and the POD for the IDLH value would be 20 ppm. In this case, no concentration response modeling was available to estimate the threshold for severe lacrimation and coughing. Application of a typical UF of 3 (See *Chapter 4*) to the NOAEL concentration of 20 ppm for mild irritation and coughing would generate an IDLH value of 7 ppm, which would be lower than appropriate based on the absence of any irritant effects at 10 ppm. Thus, in this case, since the severity of the effects at 20 ppm was not considered escape-impairing the appropriate IDLH value would be between 10 ppm and 20 ppm based on the human NOAEL with a minimal UF.

Table 3.4.2.1: Consideration of Severity of Effect

Species	Endpoint - Effect level (ppm)	Duration (minutes)	Comments
Human	NOAEL – 10	30	No irritation
Human	NOAEL – 20	30	Mild irritation and coughing
Human	LOAEL – 30	30	Severe lacrimation and coughing

3.4.2.1.2 Consideration of Lethality Data

In some cases, datasets for acute toxicity will be limited to studies reporting mortality experience in acute animal toxicology studies or from case reports from accidental human exposures from

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which a lethal concentration has been estimated. The availability of lethality data from acute toxicology studies in animals is common, and many IDLH values are derived from such data. In such cases, information on the threshold for lethality is the preferred basis for an IDLH value, rather than an estimate of median lethal concentration (i.e., the LC_{50}). Lethality thresholds can be estimated from LC_{lo} values (the lowest concentration in the study that caused lethality) if the mortality incidence is relatively low (i.e., 10% or less) or can be based on concentration-response models. These models can be used to indicate the estimated response incidence (percent response) and whether the estimate is the maximum likelihood estimate or a lower confidence limit. For example, a commonly reported model value such as an LC_{01} is the model estimated maximum likelihood concentration associated with an increased mortality incidence of 1% over control values. More recently, studies report lethality estimates using software that provides lower confidence estimates of the concentrations. For example, the USEPA provides free software for this purpose (available at http://www.epa.gov/ncea/bmds/). The output from the USEPA software is commonly reported as the benchmark concentration (BMC) for the maximum likelihood estimate or the BMCL for the 95% lower confidence limit on the concentration. Thus, a $BMCL_{05}$ is the estimated 95% lower confidence bound on the concentration associated with a 5% increased lethality response above controls.

Such model calculated values are preferred over an LC_{lo}, because they are not dependent on the actual concentrations tested and reflect the response at each concentration. Use of a lower confidence limit (i.e., the BMCL) also has the advantage of taking into account the uncertainty in the data and statistical power of the study. Frequently, the $BMCL_{05}$ (i.e., the lower 95% confidence limit on the concentration associated with a 5% response) and BMC_{01} (i.e., the central tendency estimate of the concentration associated with a 1% response) are both calculated for lethality data, and the lower value is used as the lethality threshold. The lower value is often the $BMCL_{05}$, due to the relatively wide confidence limits associated with the small sample size.

Although estimates of a lethality threshold are preferred over other measures of lethal concentrations, in many cases, the only available data from acute lethality studies are LC_{50}

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values (i.e., concentration associated with a 50% mortality incidence) [9]. If LC_{50} value estimates are available for multiple species, the lowest reliable LC_{50} value in the most relevant animal species is used for extrapolation to predicting potential human response. If no data are available that favor the use of one animal species over another, then the most sensitive species is used after considering study quality. Multiple LC_{50} values may also be available from a single study, including values for both sexes individually and for the two sexes combined. In such cases, the data are evaluated for any clear difference between the sexes. If a clear difference exists, the LC_{50} from the more sensitive sex is used. If there is no clear difference, the combined LC_{50} value is used, since the combined data provide a higher statistical power.

Table 3.4.2.1.2 illustrates different lethality data that may be available. In the example cited, three different measures of lethality are available from the rat study – the LC_{50}, LC_{lo}, and the $BMCL_{05}$. The selected POD for deriving the IDLH value would be the rat $BMCL_{05}$, because this value represents a defined response near the threshold for lethality and the data show that the rat is more sensitive than the mouse. In this case, the $BMCL_{05}$ resulted in the lowest derived value, but the $BMCL_{05}$ would generally be preferred, even if it was somewhat higher than the LC_{lo}, due to statistical variability related to the LC_{lo} and because the $BMCL_{05}$ reflects the variability in the data. The derived IDLH values reflect the application of UFs, addressing how far the data and endpoints are from the endpoint of interest. Since the goal is to estimate the threshold for the severe responses, a larger UF is applied to the LC_{50} than is applied to measures around the threshold for lethality, such as the $BMCL_{05}$ (see *Chapter 4.0* for additional discussion of UF).

[9] LC_{50} and BMC values are conceptually similar, although the BMC approach is a more recent innovation. Both values are determined by fitting a flexible mathematical curve to the data, and determining the concentration corresponding to a specified response. While various mathematical models can be fit to the data, the probit model is frequently used, as a flexible model that usually fits acute data well, particularly for lethality data (e.g., Fowles et al. [1999]).

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Table 3.4.2.1.2: Consideration of Lethality Effects

Species	Endpoint - Effect level (ppm)	Duration (minutes)	Uncertainty Factor	Derived IDLH Value (ppm)	Comments
Rat	LC_{50} – 1000	30	30	33	Males and females combined
Rat	LC_{Lo} – 400	30	10	40	1/10 died
Rat	$BMCL_{05}$ – 240	30	10	24	Modeling done by the authors
Mouse	LC_{50} – 2000	30	30	66	Males only

3.4.2.1.3 Consideration of Escape-Impairing Effects

For effects other than mortality, reported health effects in both human and animal studies are classified as severe, irreversible or escape-impairing. Identifying which effects may be escape-impairing is complicated by the fact that observed signs and symptoms within animals may differ from those expected to occur in humans. For example, the same underlying MOA that manifests as changes in respiration rate, nasal discharge or altered activity level in an acute toxicity test in animals may be reported as intolerable irritation in humans. For this reason, guidance was developed that allows for more consistent assigning of comparative severity of observed effects (i.e., severe and irreversible versus non-severe; escape-impairing versus non-escape-impairing) for commonly observed adverse effects used as the basis of IDLH values. Appendix C provides the guidelines for classifying effects commonly seen in acute animal studies.

Generally, basing IDLH values on effects that can impair escape relate to irritation responses (e.g., severe eye burning or coughing) or impacts on the nervous system (e.g., headache, dizziness, drowsiness), although other effects (e.g., cardiovascular or gastrointestinal tract effects) may be also be considered, when warranted. To facilitate a consistent approach, qualitative descriptions of severity have been developed with study results assigned to one of three categories - mild, moderate or severe. The severity and the type of the effect are

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considered in determining whether escape impairment is likely. For example, moderate to severe eye irritation, but not mild irritation, is generally considered an appropriate basis for an IDLH value based on escape impairment. For effects on the CNS, narcosis or moderate dizziness are considered sufficiently adverse to impair escape, while effects such as headache are generally not considered as an adequate basis for the IDLH value unless described in the study as debilitating or occurring with other symptoms that directly impaired vision or mobility.

Additional consideration is needed for screening assays, such as the respiratory depression 50% (RD_{50}) assay and cardiac sensitization tests. The RD_{50} assay is a sensitive measure of sensory irritation, which occurs due to stimulation of trigeminal nerve endings in the cornea and nasal mucosa. These effects frequently occur due to a decrease in respiratory frequency that occurs in some laboratory animals when exposed to chemical irritants. The RD_{50} value is considered as part of the overall weight of evidence and can be used to support the selection of a POD from other studies that identified the concentration that caused clinical signs of irritation or generated histopathology changes consistent with moderate or severe irritant effects [Alarie 1981; ASTM 1984; Schaper 1993; Nielsen et al. 2007]. The RD_{50} can also be used as the POD if no reliable LOAEL is available. However, the LOAEL is preferred over the RD_{50} as a POD because of uncertainties in relating the respiratory depression response in rodents to potential clinical or tissue changes in humans that would be correlated with severe irritation in humans [Bos et al. 1992, 2002].

Cardiac sensitization is another sensitive endpoint [Brock et al. 2003] that serves as the basis of some IDLH values. This endpoint reflects a serious effect in humans, which is characterized by the sensitization of the heart to arrhythmias. Cardiac sensitization can occur from exposure to some hydrocarbons and hydrocarbon derivatives which make the mammalian heart abnormally sensitive to epinephrine. This can result in ventricular arrhythmias and, in some cases, can lead to sudden death [Reinhardt et al. 1971]. The arrhythmia results from the hydrocarbon potentiating the effect of endogenous epinephrine (adrenalin), rather than a direct effect of exposure to the hydrocarbon. As described by NAS [2002], “the mechanism of action of cardiac

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sensitization is not completely understood but appears to involve a disturbance in the normal conduction of the electrical impulse through the heart, probably by producing a local disturbance in the electrical potential across cell membranes."

Cardiac sensitization is determined by injecting the test animal (usually dogs, but rodents are also used) with epinephrine to establish a background (control) response, followed by an injection of epinephrine during exposure to the chemical of interest. Different doses of epinephrine are often tested for the initial injection, and the dose of epinephrine chosen is the maximum dose that does not cause a serious arrhythmia [NAS 1996]. The test is very conservative, because the levels of epinephrine administered result in blood concentrations approximately 10 times the blood concentrations that would be achieved endogenously in dogs [Chengelis 1997] or humans [NAS 1996], even under highly stressful situations. Thus, even though scenarios where IDLH values would apply would be highly stressful, the cardiac sensitization test is considered a sensitive measure of a severe effect. Cardiac sensitization is relevant to humans, but because of the conditions of the assay, which focuses on the measurement of the response to a challenge injection with epinephrine, the assay itself is very sensitive [Brock et al. 2003]. The sensitivity of the assay is considered in the weight-of-evidence approach when selecting the POD and in the selection of the UF.

3.4.2.1.4 Consideration of Severe and Irreversible Effects

A variety of health effects may result from acute exposures that do not immediately impair escape (although over an extended time period these effects may be lethal). Severe adverse effects that are not immediately escape impairing are evaluated on a case-by-case basis weighing considerations, including the need for medical treatment, the potential for altered function or disability, the potential for long-term deficits in function and the likelihood for secondary symptoms that would be escape-impairing. These include severe, but reversible, acute effects such as hemolysis, chemical asphyxia, delayed pulmonary edema or significant acute organ damage (e.g., hepatitis, decreased kidney function). If a chemical is suspected of generating such effects then it is important to evaluate the design of the study to ensure that adequate time

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was allowed following completion of the exposure period, to determine whether such latent effects of interest were assessed.

Irreversible target organ effects (e.g., permanent functional respiratory impairment or permanent neurological impairment) are also considered a sufficient basis for an IDLH value. As discussed further in the following paragraphs, data on irreversible effects of special interest (e.g., reproductive and developmental toxicity) or effects that have significant latency (e.g., cancer) are generally considered as an adequate basis for the IDLH value only when single-exposure studies have been conducted that evaluated these endpoints. For example, if reproductive or developmental studies involving short-term exposures (i.e., 1 day or less) are available and have adequately long observation periods to observe delayed effects, they are considered in the development of the IDLH value; such studies can be informative regarding the potential for irreversible reproductive or developmental effects. These effects are considered in the overall weight of evidence analysis to ensure that the derived IDLH value is sufficiently protective against the most sensitive health endpoint, as described in the following paragraphs.

Standard developmental toxicity studies are not used directly because they typically involve repeated exposures (e.g., during all of gestation or from implantation through one day prior to expected parturition), and extrapolation from studies that involve long exposure periods result in an unacceptable level of uncertainty. However, it is also recognized that some developmental effects can result from exposure during a critical window of development, and that the time in which the exposure is administered may be more important than exposure duration. Therefore, data from developmental studies are evaluated in the context of the overall weight-of-evidence analysis. For example, if developmental effects are seen, the data on MOA and the relative concentration response for maternal toxicity and fetal toxicity are evaluated to determine whether an increased UF (usually by a factor of 3) is needed. Conversely, a potential IDLH value derived from systemic toxicity in the pregnant female can provide a health-protective, lower bound estimate for the IDLH value, because the exposure duration of repeated days is much longer than the duration of interest – a single 30-minute exposure. Use of repeated exposure studies in this

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manner can provide perspective to potential IDLH values derived from very high concentration acute studies where a large UF leads to relatively low IDLH values that are more than adequately protective.

Table 3.4.2.1.4 shows how developmental toxicity data can be used to help evaluate an appropriate lower bound estimate for the IDLH value. In this case, the IDLH value is derived from the 60-minute LC_{50} value, as the lowest acute lethality value from the studies of relevant duration. (See S*ection 3.5* and *Chapter 4.0*, respectively, for discussion of the adjustment for durations other than 30 minutes and UF used to calculate the derived value.) A developmental toxicity study is also available, in which exposure was for 6 hours/day on gestation days 6-20. Because the developmental effect of decreased fetal body weight may have resulted from a single exposure during a critical window, the exposure duration is listed as 6 hours. Because this is a very health protective assumption, the developmental toxicity study is not used as the basis for the IDLH value, since confidence in the actual acute exposure effect level is highly uncertain. However, the derived IDLH value does provide a lower bound estimate, since we would not expect the LC_{50}-based IDLH value to be lower than the derived value from a repeat-exposure study for non-lethal effects. The IDLH derived from the LC_{50} is somewhat higher than from the repeated-exposure developmental toxicity study; thus the overall findings are consistent with expectations and the overall dataset provides reasonable confidence in the selected value.

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Table 3.4.2.1.4: Consideration of Developmental Toxicity Data

Species	Endpoint - Effect level (ppm)	Duration (minutes)	Adjusted to 30 minutes (ppm)	Derived Value (ppm)	Comments
Rat	LC_{50} – 1800	60	2268	75.6	2/4 died – not a calculated value
Rat	LOAEL – 200	360*	458	45.8	1/21 dams died; fetal weight decreased; significant reabsorptions at 300 ppm; 6 hours/day on days 6-20 of gestation

Like developmental toxicity studies, reproductive toxicity studies tend to involve repeated exposures, and therefore usually are not used as the basis for an IDLH value. However, single-exposure reproductive toxicity studies that report irreversible or slowly-reversible effects are considered in the development of IDLH values. In addition, findings of reproductive toxicity coupled with MOA data (e.g., data suggesting an effect on hormonal control) may suggest the use of an increased UF, if the available acute toxicity data are insufficient to evaluate the concentration-duration response for such effects.

As noted above, acute animal toxicity studies rarely include sufficient post-exposure monitoring to be useful for cancer assessment. Even when a study is sufficient for evaluating carcinogenicity following a single exposure (e.g., Hehir et al. [1981]) following vinyl chloride (CAS# 75-01-4) exposure], the data are usually insufficient for a quantitative calculation of cancer risk. Therefore, concern for carcinogenicity is addressed by consideration of adding a supplemental UF (see *Chapter 4*.0) The cancer risk at the potential IDLH value can also be estimated and compared with a chosen risk level (i.e., a 1 in 1000 excess cancer risk) [NAS 2001]. The concentration corresponding to a specified risk level is not usually used as the basis for the IDLH value, due to the considerable uncertainty in extrapolating from a chronic study to

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a single exposure. However, if the estimated cancer risk at the IDLH value without the supplemental UF is below 1 in 1000, the supplemental UF is not used.

Repeated-exposure studies that identify subchronic or chronic systemic toxicity (rather than rapid onset clinical signs) are not used quantitatively as the basis for deriving the IDLH value. However, considerations of these other toxicities are included in overall database evaluation during the consideration of UF and to assess the reliability of estimates derived from acute studies. For example, if a well-conducted repeated-exposure study shows no adverse effect at a given concentration, then such a finding can help to determine the lower range of potential values for an IDLH value, since single acute exposures will usually identify a higher POD. In this way, repeated exposure studies can provide a lower bound on the range of potential IDLH values for a chemical if the databases of acute studies are limited or of marginal quality.

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3.4.2.2 Relevance of the Exposure Duration for Acute Studies

Acute animal inhalation studies reviewed for the derivation of the IDLH value may use treatment regimens ranging from an exposure duration as short as a few minutes (e.g. < 10 minutes) to several hours (e.g., 8 hours or more). Since, the intended use of the IDLH value is for the prevention of adverse effects that may occur as a result of a single exposure for 30 minutes, the derivation of an IDLH value is ideally based on:

- Studies involving exposure for 30 minutes,
- Studies that have information on the threshold for rapidly occurring escape-impairing effects, and
- Studies that include a sufficient observation period to observe potential severe delayed effects.

Acute studies of durations other than 30 minutes that provide information on escape-impairing effects and severe adverse effects are also desirable and used. Although inhalation studies of durations other than 30 minutes introduce uncertainties in extrapolating effects to a 30-minute duration, they are still used after being adjusted to a 30-minute equivalent exposure duration, as discussed in detail in Section 3.5 on Time Scaling.

It is recognized that the ideal dataset consisting of high-quality 30-minute inhalation studies with effects in the severity range of interest is often unavailable. Thus, when selecting among less than optimal study designs to identify the most appropriate critical study and POD a weight-of-evidence approach is used. For example, within a given category of studies (e.g., acute lethality studies), preference is given to high-quality studies of the duration of interest (30 minutes) or involving minimal duration extrapolation. However, the relative merits of a well-done study of longer duration vs. a poorly done 30-minute study must be considered. A well documented weight-of-evidence decision is even more important when there are no adequate acute inhalation studies in humans or animals. In such cases, holistic consideration of all other available data, including MOA information, repeated-exposure studies, studies of exposure routes other than inhalation (e.g., oral or direct injection dosing) and studies with other (usually structurally-

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related) chemicals is needed. MOA understanding is particularly important in such situations and can determine such issues as whether route-to-route extrapolation is appropriate, the impact of using data from repeated-exposure studies and which structurally-related chemicals are appropriate to use by analogy. For example, it is inappropriate to conduct route-to-route extrapolation for irritants because they target the portal of entry. In comparison, extrapolation from repeated-exposure studies may be appropriate for sensory irritants, since concentration is often a more important determinant of sensory irritation than duration.

Table 3.4.2.2 illustrates how scientific judgment is used in considering duration. In this example, only limited acute data are available for the chemical, including an RD_{50} study and one LC_{50}. However, some information on the effects of acute exposure can be extracted from clinical signs reported for a subchronic exposure study in which exposure was for 6 hours/day, 5 days/week for 13 weeks. Clinical signs reported at 4.9 ppm were limited to eyes half-closed during exposure, an indication of eye irritation, but at a level that is not escape-impairing. However, at the next higher exposure level (15.3 ppm), the authors reported burning of the nose and eyes, as well as olfactory lesions. While the lesions may have been related to the repeated exposure, it is reasonable to assume that the clinical signs of burning eyes and nose were observed during the first exposure, and that these effects would be escape-impairing. After consideration of time adjustments (see *Section 3.5*) and application of the appropriate UF (see *Chapter 4.0*), the LOAEL from the repeated exposure study was used as the basis for the IDLH value, supported by the RD_{50}. A slightly higher IDLH value would have been calculated from the LC_{50}, but that value was not used, since it involves more extrapolation due to the severity of the response (lethality). Direct observations from the initial exposure during the repeated-exposure study were considered more reliable than using the RD_{50} value directly, based on the uncertainties in interpreting the RD_{50} assay.

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Table 3.4.2.2: Use of Scientific Judgment

Species	Endpoint - Effect level (ppm)	Duration (minutes)	Adjusted to 30 minutes (ppm)	Derived Value (ppm)	Comments
Mouse	RD_{50} – 10.4	30	10.4	3.5	--
Rat	LC_{50} – 125	240	250	8.3	--
Rat	NOAEL – 4.9	360	11.2	3.7	6 hr/day, 5 d/week, 13 weeks; eyes half-closed during exposure
Rat	LOAEL – 15.3	360	35.0	3.5	6 hour/day, 5 day/week, 13 weeks; olfactory lesions, burning nose and eyes

3.4.2.3 Relevance of the Exposure Measurements

Animal inhalation studies are typically conducted using either whole-body or nose-only exposure. Both methods have strengths and limitations. Whole-body exposure more closely simulates the situation for occupational exposure and includes the potential for exposure both via inhalation and via dermal exposure to the chemical in the air. However, in rodent studies, whole-body exposure may also involve ingestion exposure that is not relevant to humans, due to grooming of fur on which the chemical has deposited. Nose-only exposure avoids the potential for ingestion exposure, but also eliminates the potential for human-relevant dermal exposure, and may place the animals under additional stress, due to their being restrained during exposure. There is no default preference for one exposure scenario over the other. Instead, the studies and results should be examined to determine whether the limitations of either method preclude the use of certain studies. For example, the observation of overt gastrointestinal (GI) effects from whole-body exposure suggests the potential for confounding by ingestion. In general, both nose-only and whole-body exposures are considered together in the overall weight-of-evidence evaluation.

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Well-conducted inhalation studies generally report both nominal concentrations (the concentration expected based on the amount of chemical introduced into the exposure system) and the analytical concentration (the amount actually measured). The two values should be similar; if they are markedly different, the reasons and implications for the difference should be determined. Large differences may reflect difficulty in maintaining the exposure atmosphere (e.g., the chemical may be adhering to the exposure chamber walls) or other issues, and may indicate poor study quality. Larger differences between nominal and analytical concentrations may be seen with static exposure studies (where the chemical is introduced into the chamber at the beginning of the experiment), as opposed to dynamic studies (where the chemical is continuously circulated and the chemical concentration is actively maintained at the target level). Because the analytical concentration reflects the actual concentration to which the animals were exposed, the analytical concentration is usually used in IDLH value calculations. However, in some cases, the nominal concentration may more appropriately reflect the exposure conditions. For example, substances, such as trichloromethylsilane (CAS# 75-79-6), sulfur trioxide (CAS# 7446-11-9), and acetone cyanohydrin (CAS# 75-86-5), react with the moisture in air to produce a variety of hydrolysis products. Table 3.4.2.3 provides examples of hydrolysis products associated with the previously listed substances. Because the observed toxicity is due to both the parent chemical and the hydrolysis products, nominal concentration is a better indicator of toxicity, since it reflects the total burden of toxic constituents, while analytical concentration would reflect only the concentration of the parent compound [NAS 2009]. In such cases, the decision of whether to use nominal or analytical concentrations depends on the approach that would be used for air monitoring and whether it would capture only the parent compound or the parent compound and its hydrolysis products.

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Table 3.4.2.3: Examples of Hydrolysis Products Associated with Selected Chemicals

Chemical Names	CAS No.	Hydrolysis products	Health effects of hydrolysis products
Trichloromethylsilane	75-79-6	Hydrochloric acid (CAS# 7647-01-0)	Respiratory tract and eye irritation
Sulfur trioxide	7446-11-9	Sulfuric acid (CAS# 7664-93-9)	Respiratory tract and eye irritation
Acetone cyanohydrin	75-86-5	Hydrogen cyanide (CAS# 74-90-8); acetone (CAS# 67-64-1)	Respiratory tract and eye irritation
Uranium hexafluoride	7783-81-5	Uranyl fluoride (CAS# 13536-84-010); hydrogen fluoride (CAS# 7664-39-3)	Respiratory tract and eye irritation

Care should also be used in considering the exposure units. For example, it is appropriate to use ppm only for gases and vapors because ppm in air refers to molecules of the chemical in air (rather than being on a weight basis). The units of mg/m^3 can be used for particulates and aerosols, as well as gases and vapors. While exposures to gases and vapors are usually reported in ppm, care is needed to ensure that units are not confused. Units of ppm can be converted to mg/m^3 using the ideal gas law. At 1 atmosphere of pressure and room temperature (25˚ C), the conversion is as follows:

$$mg/m^3 = ppm \times molecular\ weight/24.45$$

Difficulties in the determination of exposure concentrations may arise because, at high concentrations, some vapors may condense into liquid droplets, resulting in exposures to a mixture of vapor and aerosol. Under such conditions, it is generally reasonable to assume that toxicity is due to the total mass of the chemical. However, it should be recognized that vapors and aerosols (e.g., particles and liquid droplets) are deposited differently in the respiratory tractbased on many factors, including the physiochemical properties of the chemical [USEPA 1994]. For this reason, the toxicity related to vapor exposure and aerosol exposure to the same concentration (e.g., mg/m^3) of a substance may be somewhat different if respiratory tract effects are of concern.

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3.4.2.4 Other Issues of Study Relevance – Use of Surrogates and Route Extrapolation

When neither human nor animal acute inhalation data are sufficient to derive an IDLH value for a chemical of interest, other approaches are considered, depending on the understanding of the MOA and availability of data. Available information on surrogates, or related compounds, primary metabolites, or key breakdown products (e.g., secondary chemical products formed from hydrolysis due to moisture in the air) that are closely related to the chemical of interest, can be used when inadequate information is available for the chemical of interest. As an example of the use of a related compound during the derivation of an IDLH value, bromine pentafluoride (CAS # 7789-30-2) and chlorine pentafluoride (CAS# 13637-63-3) differ only in the primary halogen atom. Because of their similarities, bromine pentafluoride can be used as a surrogate for chlorine pentafluoride and the limited toxicity data available for bromine pentafluoride indicates that its toxicity is comparable to, or slightly less than, that of the chlorine compound. Another example is the assessment of the acute inhalation hazard of an entire chemical class based on the data associated for a single compound; the NAS/NRC drafted AEGL values for multiple chlorosilanes and metal phosphides use this approach [NAS 2007, 2009]. This approach takes advantage of knowledge about the MOA and the actual form of the toxicity of related chemicals to use the entirety of the data for the class of chemicals to develop exposure values. For example, for the chlorosilanes the primary cause of the acute effect of interest (irritation) is hydrolysis in most air to form hydrogen chloride. Thus, for the series of related chlorosilanes, the IDLH value can be derived based on actual testing data for the most data-rich member of the family and adjusting the IDLH value for other members based on the respective amounts of chlorine atoms produced during hydrolysis. A refinement of the use of surrogate chemicals or information on classes of related chemicals is to use information on the relative potency when adequate data are available to quantitatively compare the chemical of interest with the surrogate, but data for the chemical itself are not sufficient to develop an IDLH value. In such cases, the toxicity threshold is much better understood for the surrogate than for the chemical of interest, but the threshold for the chemical of interest can be adjusted based on relative potency.

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When a surrogate or relative potency approach is used it is necessary to consider the uncertainties associated with using a limited database for the chemical of interest versus the uncertainties associated with extrapolation from a surrogate chemical. As an example of extrapolation from a breakdown product, acetone cyanohydrin spontaneously dissociates into HCN (CAS # 74-90-8) and acetone (CAS# 67-64-1), with the acute toxicity being driven by exposure to an equimolar (i.e., having an equal number of moles) equivalent to HCN, which can serve as a surrogate [NAS 2002, 2005]. Use of such surrogates is not necessary when adequate information on the primary chemical is available. In addition, if a surrogate is being considered as the basis for the IDLH value, it is important to consider whether other aspects of toxicity are associated with the parent chemical and whether these aspects are adequately addressed by the surrogate. For example, acetone cyanohydrin causes irritant effects that are not seen with exposure to HCN, but the most potent escape-impairing effects are secondary to cyanide action as a metabolic toxicant. This results in HCN being the most valid surrogate for acetone cyanohydrin.

If no adequate inhalation data are available for the chemical of interest or for a potential surrogate, an IDLH value may be derived by extrapolation from studies that used exposure routes other than inhalation, such as oral or intraperitoneal (i.p.) dosing studies. As noted above, this route-to-route extrapolation is appropriate only if the effect of interest is systemic (i.e., involves absorption into the systemic blood circulation for distribution to an internal target tissue). Route extrapolation (e.g., from oral or i.p. dosing studies) is not appropriate if the chemical's primary relevant effects for IDLH development are as an irritant, or if it is expected to target the respiratory tract as the most sensitive end point. The ideal approach is to use a physiologically-based pharmacokinetic (PBPK) model to conduct the route-to-route extrapolation, but it is rare that such data would exist (particularly for a chemical for which the inhalation data are insufficient to directly derive an IDLH value). In the absence of such a PBPK model, the approach is to estimate the concentration to which a 70-kg worker could be exposed in order to receive the equivalent *systemic* dose to that delivered in the oral or i.p. study. The 30-

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minute concentration is estimated by multiplying the animal dose data by the worker body weight (to reach a systemic dose), and dividing by the volume of air inhaled air per work day as shown in the equation below:

$$\textit{Systemic dose [mg/10m}^3\textit{]} = \frac{\textit{oral or i.p. dose [mg/kg] x 70 kg}}{\textit{10 m}^3}$$

This conversion is a health protective estimate of the air concentration that would result in the systemic dose, since a worker breathing at a rate of 50 L/minute for 30 minutes would inhale 1.5 m^3 of air; dividing by 1.5 instead of 10 m^3 would result in a substantially higher number. Quantitatively, this approach assumes that toxicity is related to the total systemic dose (e.g., area under the time-concentration curve), rather than peak internal dose. However, qualitatively, since acute oral and i.p. studies typically involve a single bolus exposure, they may bear a closer resemblance to the 30-minute exposure than a full-day exposure. In light of this consideration, it is likely that this approach would be health protective, even though acute toxicity is often related to peak concentrations in blood or tissue.

A second consideration in applying route-to-route extrapolation is the impact of first-pass metabolism. First-pass metabolism refers to the metabolism of the material delivered from the GI tract directly to the liver via hepatic blood flow, before distribution to the general systemic circulation. First-pass metabolism by the liver would decrease systemic exposure to the parent chemical following oral exposure compared to inhalation exposure (and increase the exposure at sites other than the liver to the metabolites formed in the liver). First-pass metabolism by the respiratory tract tends to be of smaller magnitude than for the liver, but would have the opposite effects on target tissue doses at remote sites. Quantitatively addressing the implications of first-pass metabolism is often difficult, and use of a surrogate for which inhalation data are available is considered to provide greater weight of evidence for chemicals where first-pass metabolism plays an important role. Comparing IDLH values derived using different approaches (e.g., using a surrogate versus using route-to-route extrapolation) can provide information on possible uncertainties involved and may help to set the range of reasonable IDLH values. Finally, since

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this approach is based on systemic dose, it assumes equal absorption via both routes (unless a separate correction is made) and ignores issues related to the physical characteristics of the chemical (e.g., gas/vapors versus particulate) and implications of particle size and dosimetry (i.e., determination of respiratory tract region deposition fractions). Where quantitative adjustments for differing routes of exposure are uncertain, this issue is further considered in the selection of additional UFs. Additional considerations for conducting route-to-route extrapolations are described in several guidance documents [e.g., USEPA 1994; NAS 2001].

3.5 Time Scaling

A critical consideration in developing IDLH values is accounting for exposure duration and the extrapolation from the experimental exposure duration to the duration of interest (i.e., 30 minutes). The methods used for doing these extrapolations in the development of IDLH values are similar in many ways to the Standing Operating Procedures (SOP) outlined by the NAS for the development of AEGLs [NAS 2001]. Issues to be considered include evaluation of the chemical's MOA and how that is reflected in key drivers of toxicity (concentration vs. time); modifications to Haber's rule; and methods for calculating "n" in the ten Berge modification to Haber's rule. These issues are discussed briefly in the following paragraphs, and in more detail in NAS [2001].

The toxicity of airborne chemicals depends on both exposure concentration and exposure duration as well as physiochemical properties that affect respiratory deposition and systemic absorption. Ideally, information from validated PBPK or biologically-based dose-response (BBDR) models is used for time extrapolation, but such information is rarely available. In the absence of such models, simpler concentration-time relationships are used. Historically, particularly for extended exposure durations, toxicity was described as the simple product of concentration (Conc) and time, so that (Conc x time = k), a constant. In other words, if ($Conc_1$ x $time_1$) = ($Conc_2$ x $time_2$), the toxicity would be the same. This relationship is described as Haber's law, or Haber's rule [Haber 1924].

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The key assumption embedded in the relationship of Haber's rule is that damage (or depletion of protective tissue response) is irreversible and therefore, that toxicity is cumulative, related to the total dose of the chemical [NAS 2001]. This assumption is generally not true for acute exposures [NAS 2001]. For example, toxicity due to asphyxiants, (e.g., argon or nitrogen), is related to the peak concentration of the chemical, rather than the cumulative dose.

Further investigation into the relationship between concentration, duration and toxicity was conducted by ten Berge et al. [1986], who proposed the following relationship between Conc and duration (time, t): ($Conc^n \times t = k$). These investigators examined the data on 20 irritant and systemically-acting gases and vapors; the results of this investigation indicated that n was ≤ 3 for lethality data from 18 of the 20 chemicals. This study is one of the primary published sources for values of "n." Furthermore, based on the finding in this study that an "n" of 3 covers 90% of the chemicals in the dataset, the default value of an "n" for extrapolating from longer durations to shorter durations was chosen to be 3, as a health-protective approach.

The following approach is used in extrapolating across durations for development of IDLH values:

1. No extrapolation is needed if the study of interest involved exposure for 30 minutes; the empirical data are used directly.
2. If information on the value of "n" is available from the original paper of ten Berge et al. [1986], or from authoritative reviews (e.g., AEGL documents), that value is used. Note, however, the comments in Section 3.5.2 describe caveats to the use of the ten Berge data, and other considerations in the choice of "n."
3. If no value of "n" is available, "n' can be mathematically derived, as described in Section 3.5.1.
4. If the data are not available to support the derivation of "n," a default of 1 is used if the duration of the study of interest is less than 30 minutes, in which case the ten Berge equation defaults to Haber's rule. Conversely, if the duration of the study of interest is more than 30 minutes, the default of 3 is used for "n."

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The impact of the value of "n" on the shape of the concentration-time-response curve is shown in Figures 3.5.1 and 3.5.2. As shown in these figures, larger values of "n" result in flatter curves, meaning that, for a given degree of toxicity, the concentration varies less with changes in duration. This is particularly apparent in Figure 3.5.1, which shows the extrapolation from 4 hours to 30 minutes. This figure shows the impact of using different values of "n" to extrapolate to shorter durations from a concentration of 10 ppm at 4 hours. In this example, an "n" of 3 results in a concentration at 30 minutes that is not much higher than the test concentration at 4 hours, while the calculated concentration at 30 minutes is substantially higher when n = 1. Thus, using n = 3 for extrapolating from longer durations to 30 minutes results in lower concentrations, a more health-protective approach.

Figure 3.5.2 shows the converse situation, extrapolating from an exposure to 10 ppm for 15 minutes to longer durations. In this case, the steeper curve associated with n = 1 results in a lower concentration at 30 minutes, compared with the value calculated using n = 3. Thus, using n=1 is a more health-protective approach in extrapolating from shorter durations to 30 minutes.

Based on these considerations, a default value of n = 1 is used for extrapolation from shorter durations, and a default value of n = 3 is used for extrapolation from longer durations to the 30-minute duration of interest. In both cases, a calculated "n" specific to the chemical and species of interest is used when data are available to calculate the value.

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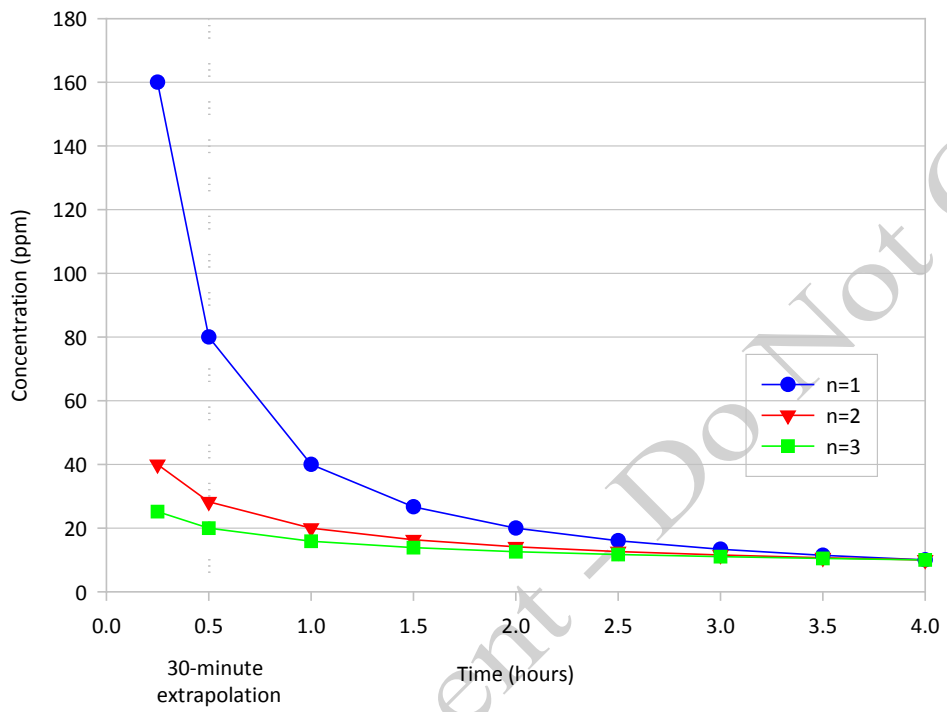
Figure 3.5.1 ten Berge Extrapolation from Longer (4 hours) to Shorter (30 minutes) Durations



The data used to construct Figure 3.5.1 are shown in Table 3.5.1. Table 3.5.1 shows the calculated concentrations when extrapolating from 10 ppm at 4 hours, using "n" values of 1, 2, or 3.

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Table 3.5.1: Time Scaling for 10 ppm at 4-Hours

Time	n = 1	n = 2	n = 3
0.25	160	40	25
0.5	80	28	20
1	40	20	16
1.5	27	16	14
2	20	14	13
2.5	16	13	12
3	13	12	11
3.5	11	11	10
4	10	10	10

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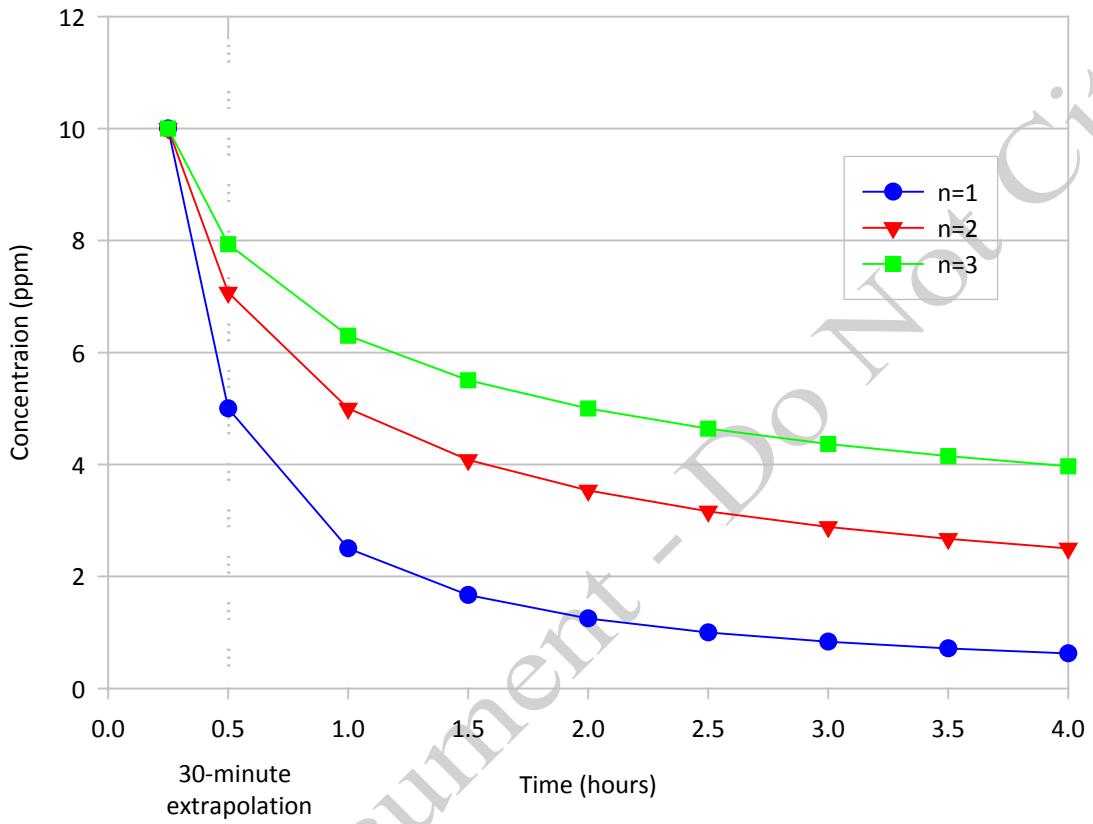
Figure 3.5.2: ten Berge Extrapolation from Shorter (15 minutes) to Longer (30 minutes) Durations



The data used to construct Figure 3.5.2 are shown in Table 3.5.2. Table 3.5.2 shows the calculated concentrations when extrapolating from 10 ppm at 0.25 hours, using "n" values of 1, 2, or 3.

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Table 3.5.2: Time Scaling for 10 ppm at 15-minutes (0.25-Hours)

Time	n = 1	n = 2	n = 3
0.25	10	10	10
0.5	5	7	8
1	3	5	6
1.5	2	4	6
2	1	4	5
2.5	1	3	5
3	1	3	4
3.5	1	3	4
4	1	3	4

The following paragraph illustrates the effects of time scaling on inhalation toxicity data evaluated during the development of IDLH values for three chemicals:

- 1,1-Dimethylhydrazine,
- Vinyl acetate, and
- Titanium tetrachloride.

In the first example, the identified LC_{50} and LOAEL values for 1,1-dimethylhydrazine correlated to exposure durations of 5 or 15 minutes. No empirically derived "n" values were identified within the reviewed literature for 1,1-dimethylhydrazine. Since the selected data were associated with exposure times less than 30 minutes, a default value of 1 for "n" within the ten Berge equation was applied based on the rationale discussed in the previous paragraphs to extrapolate the most health protective estimate. Time scaling resulted in a reduction of the exposure concentrations to approximately 17 to 50% of the original exposure concentrations for the 5 and 15 minute durations, respectively. Table 3.5.3 provides the extrapolated 30-minute equivalent concentration for 1,1-dimethylhydrazine. In comparison, the selected LC_{50} and LOAEL values for vinyl acetate were associated with exposure durations of 2 to 6 hours. Because no empirically derived value of "n" was available, a default value of 3 for "n" was used for time scaling in the ten Berge equation to adjust the data points from longer to shorter exposure durations. As noted earlier, this is a health-protective default. The resulting extrapolated concentrations were approximately double the original exposure concentrations and can be found

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in Table 3.5.4. The last example, titanium tetrachloride (See Table 3.5.5), demonstrates the effects of the use of an empirically derived "n" to calculate the 30-minute equivalents for exposure concentrations associated with durations both shorter and longer than 30 minutes. A value of 0.88 has previously been calculated by the NAS during the development of the AEGL values for titanium tetrachloride [NAS 2007]. For data corresponding to exposure durations less than 30 minutes, the resulting extrapolated concentrations were approximately 5 to 50 % of the original LC_{50} and LOAEL values. Substantial changes in the extrapolated 30-minute equivalent concentrations were also observed when extrapolating from longer to shorter durations, with the relative increases being in a range of 2 to 10 times higher than the original value. As evident by the three previous examples, selection of the appropriate "n" during time scaling may greatly affect the resulting 30-minute equivalent concentrations.

Table 3.5.3: Time Scaling of Toxicity Data from Shorter to Longer Durations Using the ten Berge Equation – 1,1-Dimethylhydrazine (CAS No. 57-41-7)

			Toxicological Endpoint				
Study No.	**Species**	**Reference**	**LC50 (ppm)**	**LOAEL (ppm)**	**Exposure Duration (min)**	**n**	**30-Minute Equivalent Value (ppm)**
1	Rat	Weeks et al. [1963]	8230		15	1	4115
2	Rat	Weeks et al. [1963]	24500		5	1	4083
3	Dog	Weeks et al. [1963]	3580		15	1	1790
4	Dog	Weeks et al. [1963]	22300		5	1	3717
5	Dog	Weeks et al. [1963]		360	15	1	180
6	Dog	Weeks et al. [1963]		1550	5	1	258

LC_{50} = The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; LOAEL = lowest observed adverse effect level; min = minutes; n = exponent applied within ten Berge equation [1986]

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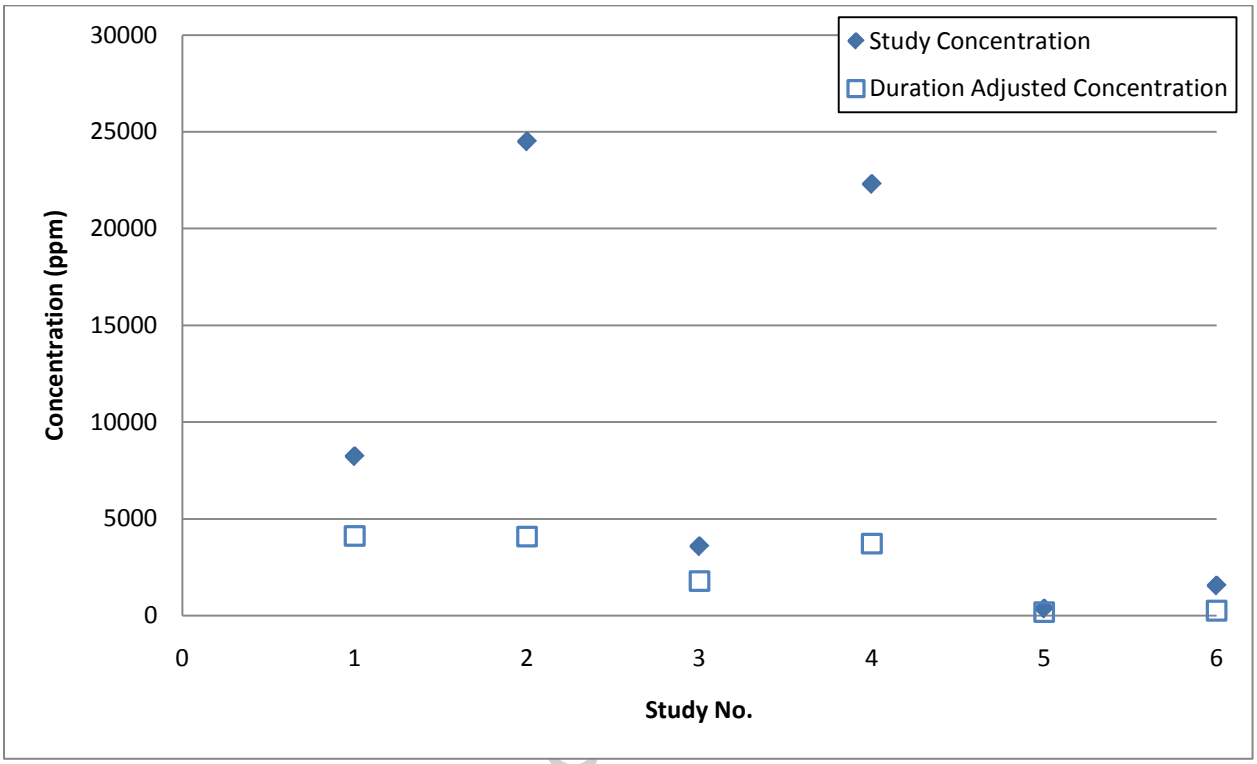
Figure 3.5.3: Time Scaling of Toxicity Data from Shorter to Longer Durations Using the ten Berge Equation – 1,1-Dimethylhydrazine (CAS No. 57-41-7)



All 30-minute data points are duration adjusted values.

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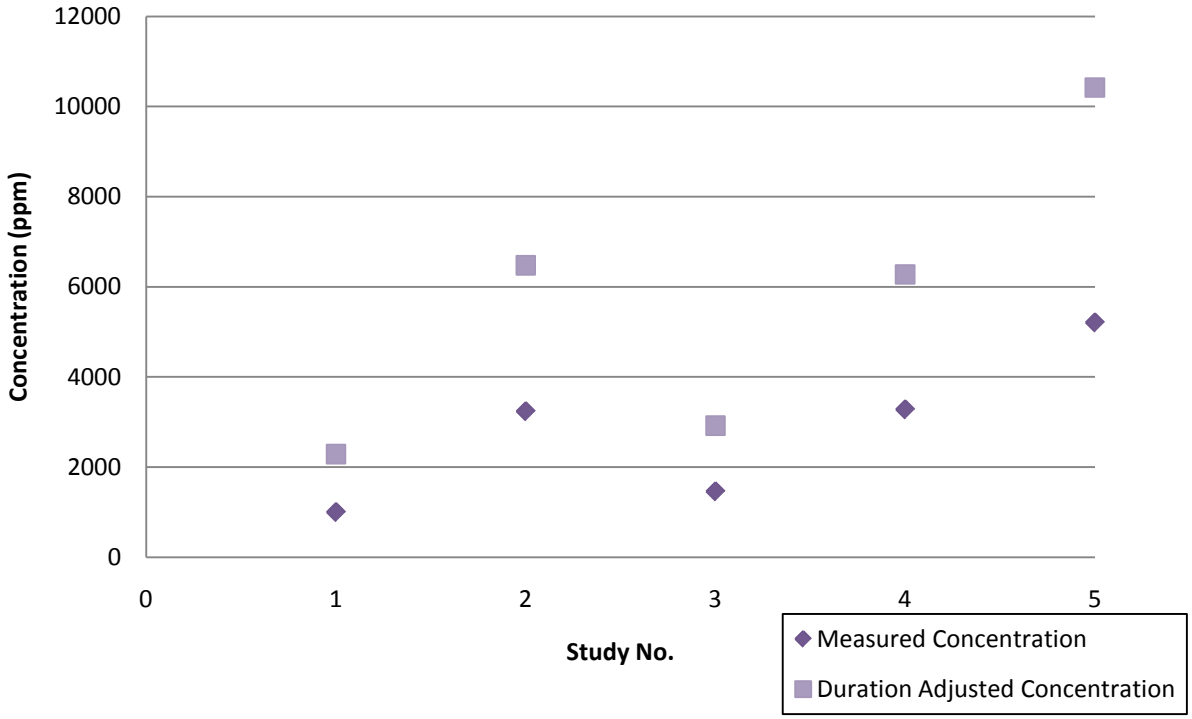
Table 3.5.4: Time Scaling of Toxicity Data from Shorter to Longer Durations Using the ten Berge Equation – Vinyl Acetate (CAS No. 108-05-04)

Study No.	Species	Reference	Toxicological Endpoint LC_{50} (ppm)	Toxicological Endpoint LOAEL (ppm)	Exposure Duration (min)	n	30-Minute Equivalent Value (ppm)
1	Rat	Bogdanffy et al. [1997]		1000	360	3	2289
2	Rat	Roumiantsev et al. [1981]	3238		240	3	6476
3	Mouse	Smyth and Carpenter [1973]	1460		240	3	2920
4	Dog	Smyth and Carpenter [1973]		3280	210	3	6274
5	Guinea Pig	Smyth and Carpenter [1973]	5210		240	3	10420

LC_{50} = The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; LOAEL = lowest observed adverse effect level; min = minutes; n = exponent applied within ten Berge equation [1986]

Figure 3.5.4: Time Scaling of Toxicity Data from Shorter to Longer Durations Using the ten Berge Equation – Vinyl Acetate (CAS No. 108-05-04)*



*All 30-minute data points are duration adjusted values.

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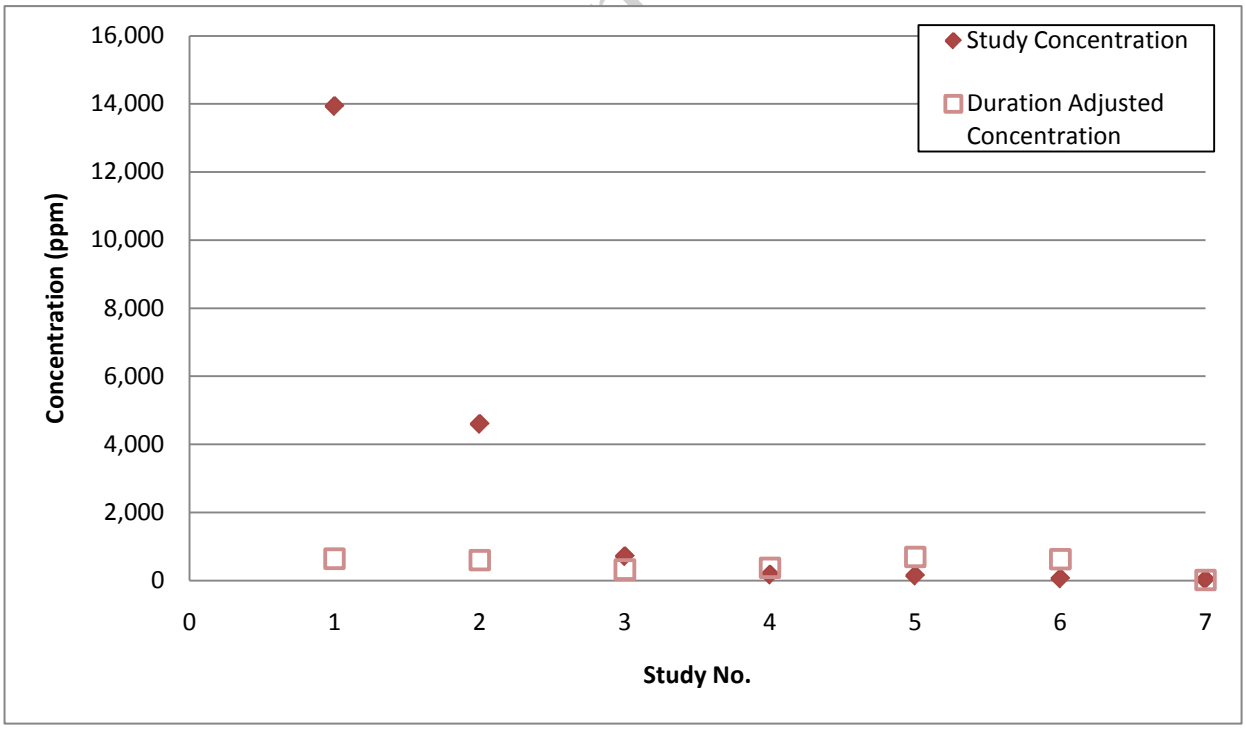
Table 3.5.5: Effects of an Empirically-Derived "n" on Time Adjustments Using the ten Berge Equation – Titanium Tetrachloride (CAS No. 7550-45-0)

Study No.	Species	Reference	Toxicological Endpoint LC_{50} (ppm)	Toxicological Endpoint LOAEL (ppm)	Exposure Duration (min)	n†	30-Minute Equivalent Value (ppm)
1	Rat	Kelly [1980]	13,940		2	0.88	642
2	Rat	Kelly [1980]	4600		5	0.88	600
3	Rat	Kelly [1980]	713		15	0.88	324
4	Rat	Kelly [1980]	171		60	0.88	376
5	Rat	Kelly [1980]	143		120	0.88	691
6	Rat	Kelly [1980]	59		240	0.88	627
7	Rat	Gardner [1980]		26	20	0.88	16

LC_{50} = The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; LOAEL = lowest observed adverse effect level; min = minutes; n† = exponent applied within ten Berge equation [1986]; [NAS 2007]

Figure 3.5.5: Effects of an Empirically-Derived "n" on Time Adjustments Using the ten Berge Equation – Titanium Tetrachloride (CAS No. 7550-45-0)*



*All 30-minute data points are duration adjusted values.

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Chapter 4.0 Use of Uncertainty Factors

4.1 Application of Uncertainty Factors

As noted in prior sections of this CIB, the first step in the development of an IDLH value is to determine POD estimates adjusted to a 30-minute equivalent exposure. However, in most cases the available POD values need to be further adjusted to develop an IDLH value that protects workers from potential lethal, severe or irreversible, or escape-impairing health effects. Thus the IDLH value can be represented as:

$$\textit{IDLH Value} = \frac{\textit{POD (e.g., 30-min equivalent } LC_{50}, LC_{lo}, \textit{ LOAEL, or NOAEL)}}{\textit{Total Uncertainty Factor}}$$

The application of UFs is needed to account for uncertainties related to extrapolation from the concentration that caused effects in the selected toxicity study to those that would be expected to be below the threshold for such effects in workers exposed for up to 30 minutes. For example, if the most appropriate POD was an LC_{50} in rats from a 30-minute exposure study, then use of this value directly as the IDLH value would clearly not be acceptable since a sub-threshold concentration for humans is needed. Dividing the selected POD, such as the LC_{50} in this example, by an additional UF would then reduce the IDLH value to a lower concentration well below the LC_{50}.

In general, the UFs need to address all key areas of uncertainty that result from extrapolating from the available studies. Most organizations that develop exposure values/limits consider the following key areas of uncertainty:

- Interspecies variability in sensitivity: This area addresses differences in sensitivity between the test species (e.g., mouse, rat, etc.) and the average human for the population of interest (i.e., in the context of IDLH application, workers).

- Human variability in sensitivity: This area addresses differences in sensitivity between the average human from the population of interest to the sensitive component of the population of interest.

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- Severity of effect: Since the IDLH value is intended to be below a concentration that will cause death or severe, irreversible, or escape-impairing effects, the UF needs to account for extrapolation from a POD that caused such responses in the selected toxicology study to a concentration below the threshold for these effects.

- Duration of exposure: Some organizations that develop exposure values/limits include consideration of the duration of the study that served as the POD in the UF determination and its relevance to the duration of interest. In the context of IDLH development, this area of uncertainty is not of concern because duration extrapolations are small and accounted for in the adjustment to the POD.

- Other database deficiencies: When datasets available to develop IDLH values are very limited, it is necessary to account for the possibility that the available studies did not identify the most sensitive endpoint relevant to IDLH development. In such cases it is appropriate to increase the UF to account for this uncertainty.

An approach used by many organizations, such as used by USEPA for developing reference concentrations [USEPA 1994] and for the AEGL process [NAS 2001], involves consideration of these separate areas of uncertainty and the multiplication of UFs for each of these areas to derive the final cumulative UF.

The NIOSH IDLH methodology is a modification of this approach that blends the rigor of full consideration of the relevant areas of uncertainty embedded in the USEPA and AEGL approaches with the flexibility to fully use the limited data from multiple lines of evidence often encountered in IDLH development. Overall, the assignment of UFs for IDLH derivation includes two steps:

1. Selection of an appropriate preliminary UF range, and

2. Modification of this preliminary range to select a final value.

The preliminary UF ranges are based on consideration of the study design and the adverse health effect occurring at the POD. Use of a preliminary range of values helps to ensure consistency in application of UFs within the IDLH development effort for diverse chemicals. However, modification of the UF is often required based on the unique issues arising from the review of

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the database for each unique chemical. Thus, the current approach captures the need to apply a consistent approach for UF application while maximizing the ability to make informed decisions based on weight-of-evidence considerations.

4.2 The NIOSH IDLH Value Uncertainty Factor Approach

As discussed regarding the overall UF approach**,** the analysis focuses on the weight-of-evidence approach using all the relevant data. Thus, a range of preferred UFs is shown for each of the typical types of effect levels that are available as a POD. However, the actual UF applied is determined based on the weight-of-evidence evaluation for each chemical that allows for modifying the preferred UF based on additional considerations unique to the dataset. The preferred UF ranges are shown in Table 4.2.1. The most common UFs for a given data type are shown, but the range indicates how this value is commonly adjusted up or down based on the entirety of the database as described further below. The UFs typically are applied as multiples of 1 or 10, and using an intermediate value of 3. The value of 3 represents a one half of $\log_{10}$ unit (3.16 rounded to 3) as the minimum increments that are used for the UF adjustments to reflect the level of precision for such an approach.

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Table 4.2.1: Typical Uncertainty Factor Ranges

Point of Departure	Preferred Uncertainty Factor (UF)	Typical UF Range
LC_{50} (in an animal study)	30	10 to 100
LC_{01}, LC_{Lo}, or $BMCL_{10}$ for lethality in animals	10	3 to 30
LC_{Lo} in humans	3	1 to 10
LOAEL for an escape impairing or irreversible effect in animals	10	3 to 30
NOAEL for an escape impairing or irreversible effect in animals, or animal RD_{50}	3	1 to 10
LOAEL for an escape impairing or irreversible effect in humans	3	1 to 10
NOAEL for an escape impairing or irreversible effect in humans	1	1 to 3

Selection of values other than the preliminary UF for deriving an IDLH value is common, reflecting the use of a weight-of-evidence approach and the sometimes-conflicting data from multiple lines of evidence. Common situations that lead to movement away from the preliminary UF value relate to evaluation of data for the areas of uncertainty and extrapolation noted in the prior section.

- Interspecies variability in sensitivity: If chemical-specific data are available to help determine the magnitude of the differences in species sensitivity, then such data are used to refine the size of the final UF. For example, if information about specific sensitivity due to differences in species metabolism is available, the UF applied to the POD from an animal study is adjusted accordingly (either up or down depending on the data). If health effects data that serve as the POD are from human studies, then the UF would not need to address this area of uncertainty.

- Human variability in sensitivity: If chemical-specific data are available to help determine the magnitude of the variability in human sensitivity, then such data are used to refine

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the size of the final UF. If health effects data that serve as the POD are from a sensitive human group (e.g., non-smoking, young adult females for a clinical study of nasal irritation [Shusterman et al. 2003]), then the UF would be smaller in addressing this area of uncertainty. Since IDLH values are used in worker-health applications, the range of variability that needs to be covered in applying the UF is expected to be less than for development of exposure values/limits meant to protect sensitive members of the general public.

- Severity of effect: The size of the adjustment needed would reflect the severity of effect observed at the POD. This is reflected in the preliminary UF ranges shown in Table 4.2.1. For example, as shown in the table, to derive an IDLH that protects from severe effects, a larger margin would be needed between an LC_{50} and the IDLH than would be needed in between a $BMCL_{05}$ for an escape-impairing effect and the IDLH value. The range of preferred values incorporates this consideration of effect severity.

  The consideration of the severity of effect also addresses the slope of the concentration-response curve. Steep concentration- response curves and high-quality data may result in UFs at the lower end of the range. Steep concentration response curves represent estimates of responses that decrease rapidly with decreasing exposure concentrations, so that a smaller UF may be warranted to reach the response level in the concentration-response curve, compared with a more shallow concentration-response curve. Thus, if the concentration-response curve is very steep, a factor of 10 (rather than the preliminary UF of 30) may be applied to an LC_{50}, based on a consideration of the overall database. This is because there is less than a factor of 3 between the LC_{50} and the (actual or estimated) LC_{01}.

- Duration of exposure: For most acute limits, including for IDLH development, acute studies are typically used directly as the basis for the POD. Thus, the available studies are generally representative of the overall duration of interest (exposure for a single day or less). Further refinements to account for uncertainties in duration extrapolation, such

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as between a 4-hour study and the 30-minute duration of interest for IDLH development, are addressed in the time-scaling adjustment to the POD (see *Section 3.5*), rather than as a consideration for the UF value. However, significant uncertainties may need additional consideration if the available study is limited in design or outside the immediate duration range of interest. For example, if only repeat-exposure studies were available for a chemical to serve as the POD, and the observed effects were not clearly due only to initial acute exposures, the use of such a POD might justify a smaller UF.

- Other database deficiencies: An UF at the higher end of the typical range (e.g., the use of a UF of 10 instead of 3) is often used if major uncertainties or additional significant concerns are identified. If a database is very deficient, then the UF might be increased. This approach is often used if the only reliable data are lethality data from a single acute study. Other considerations for database deficiency relate to the potential for effects that were not evaluated in the available studies. For example, the higher end of the range may be used if the data indicate that the chemical is a sensory irritant and the data are insufficient to derive an IDLH value (e.g., due to inappropriate exposure durations), but indicate a large margin between concentrations causing severe irritation and those causing death. Other data gaps that may affect the size of the overall UF reflect specific endpoints of concern. For example, a UF from the higher end of the range may be used if a chemical is a known or likely carcinogen or a developmental toxicant, with evidence that acute exposures may be of concern.

The examples in Appendix A highlight how these weight of evidence considerations are applied to select a UF and derive the IDLH value.

4.3 Research Support for the NIOSH UF Approach

The uncertainty factor approach used for deriving IDLH values is based on a review of approaches used by other organizations that establish acute exposure limits/values, NIOSH research efforts, and other independent research.

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The NIOSH approach is similar to that of other agencies in terms of the areas of uncertainty accounted for in determining the appropriate value of the total UF. Although the NIOSH approach does not assign an individual factor for each area of uncertainty, there is generally good agreement between the NIOSH UF and the UF embedded in derivation of AIHA ERPG values and the cumulative UF used for derivation of the AEGL values. As expected, there is not complete alignment between these values because of differences in application of IDLH values versus other types of acute exposure limits. In particular, the UF applied to the IDLH value is often smaller than for deriving the ERPG or AEGL values, which results in a larger final exposure limit for IDLH values compared to these other guidelines. For example, differences often arise due to the explicit inclusion of potentially sensitive members (e.g., children, elderly, and individuals with health impairments) of the general population during the establishment of community-based acute exposure limits, such as the ERPG and AEGL. The IDLH values do not take into consideration the potentially sensitive members of the general population because it is assumed that they will not be substantially represented in the workforce for the purposes of considering average population responses. However, in some cases such populations may be considered when a chemical has specific effects on a target population that is well-represented in the expected worker population. An example would be an agent that has significant impacts on asthmatics. In such cases, health effects data from asthmatics that have been exposed to the agent would be appropriate for defining the POD as the basis for deriving an IDLH value

To further verify that the preliminary ranges of the UF are supported by existing data, NIOSH conducted an analysis of acute toxicity data to determine the appropriate size of the UF for extrapolating from various points of departure to derive IDLH values that would be expected to protect from lethal, severe, irreversible or escape-impairing effects in humans. Two approaches were used: one based on a detailed evaluation of acute toxicity data for 20 chemicals, and the second based on data for 94 chemicals taken from the documentation for current IDLH values and consideration of MOA.

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From these data compilations for chemicals with robust datasets, the ratios between animal lethality values commonly used as the POD for developing the IDLH value (e.g., LC_{50} values) and the effect level for lethality or other non-lethal effects in humans were determined for each chemical. The distribution of these ratios was analyzed and the median value and 95th percentile value for each comparison were derived (See *Appendix D*). The resulting median values and upper bound estimates for these case study chemicals were used to verify that the range of total UFs adopted in the IDLH methodology adequately accounts for the value that should be applied to an animal-based endpoint to protect from severe or escape-impairing effects in humans.

The analysis found that animal lethal concentrations and human effect thresholds (both LC_{lo} values and LOAELs for severe or escape-impairing effects) were generally correlated, such that chemicals with low animal LC_{50} values tended to have low human lethality thresholds and cause severe or escape-impairing effects in humans at low concentrations. This finding was important to support the approach of developing preliminary UF ranges that could be used to address protection from non-lethal effects when extrapolating from data from acute animal studies. Additional analyses were conducted by MOA category (e.g., irritant, CNS depressant, or "other") to determine if different UF ranges could be applied based on a chemical's MOA. However, statistically significant differences were not found among the MOA categories. Thus, this further refinement to the approach for developing a preferred UF to address effect severity by MOA category has not been applied for IDLH derivation. Overall, comparison of the median values to the UF ranges in Table 4.2.1 showed that the most common value is typically above or in the range of the median value for the comparison dataset. This result is also consistent with other evaluations that analyzed effect level ratios from acute toxicity studies [e.g., Rusch et al. 2009]. Additional results, as well as the results of the second approach, are presented in Appendix D.

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Appendix A - Example of the Derivation of an IDLH Value

This appendix illustrates the IDLH value derivation based on the scientific criteria outlined in this document. This profile contains an IDLH value and supporting documentation for vinyl acetate (CAS No. 108-05-4). It should be noted that the presented information is intended to serve only as an illustration of the application of the derivation process outlined in this CIB. The proposed IDLH value for vinyl acetate presented in this CIB should not be construed as official NIOSH policy.

A.1 Overview of the Proposed IDLH Value for Vinyl Acetate

IDLH value: 100 ppm (352 mg/m^3)

Basis for IDLH value: The IDLH value is based on the LC_{50} of 1460 ppm for a 4-hour exposure in mice [Smyth and Carpenter 1973] was used to derive an IDLH value. The LC_{50} was adjusted to a 30 minute exposure duration of 2920 ppm. An uncertainty factor of 30 was applied to account for extrapolation from a concentration that is lethal to animals, animal to human differences and human variability, resulting in an IDLH value of 97 ppm (rounded to 100 ppm).

A.2 Supplemental Information relating to Vinyl Acetate

Original (SCP) IDLH value: None

Basis for original (SCP) IDLH value: None

NIOSH REL: 4 ppm (15 mg/m^3), 15-minute

Current OSHA PEL: Not available

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1989 OSHA PEL:[10]	Not available
2007 ACGIH TLV:	10 ppm, TWA; 15 ppm, STEL
2007 AIHA ERPG:	ERPG-1: 5 ppm; ERPG-2: 75 ppm; ERPG-3: 500 ppm
2007 AIHA WEEL:	Not established
Description of substance:	Colorless liquid with a pleasant, fruity odor.
LEL:	26,000 ppm; (10% LEL = 2600 ppm)
NAC AEGL:	National Advisory Committee [2007] Interim Acute Exposure Guideline Levels (AEGLs): Vinyl Acetate, CAS No. 108-05-4

Table A.2: Summary of the AEGL Values for Vinyl Acetate

Classification	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm
	24 mg/m^3	24 mg/m^3	24 mg/m^3	24 mg/m^3	24 mg/m^3
AEGL-2	230 ppm	230 ppm	180 ppm	110 ppm	75 ppm
	810 mg/m^3	810 mg/m^3	630 mg/m^3	390 mg/m^3	260 mg/m^3
AEGL-3	760 ppm	760 ppm	610 ppm	380 ppm	250 ppm
	2700 mg/m^3	2700 mg/m^3	2100 mg/m^3	1300 mg/m^3	880 mg/m^3

mg/m^3 = milligrams per cubic centimeter; ppm = part per million

A.3 Summary of Available Animal and Human Data

A.3.1 Animal data

Lethal concentrations of vinyl acetate were identified in rats, mice, rabbits and guinea pigs. In 4-hour exposures to vinyl acetate, Smyth and Carpenter [1973] reported LC_{50} values for different species varying by a factor of 3.6, ranging from 1460 ppm in mice, 2760 ppm in rabbits, 3680 ppm in rats, to 5210 ppm in guinea pigs. These data indicate that mice are substantially more

[10] 1989 PELS are no longer a federal OSHA policy, but many of these PELs were adopted by state OSHA plans, thus the 1989 PELs may still be in force in various states.

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sensitive to vinyl acetate than other species. In all species, deaths were due to pulmonary distress, including congestion and hemorrhaging. The greater sensitivity of mice was also supported by the results of Roumiantsev et al. [1981], who reported a 4-hour LC_{50} in rats of 3238 ppm, and a 2-hour LC_{50} in mice of 3010 ppm.

Limited data describing non-lethal effects of vinyl acetate exposure were identified. In a single-exposure study that was part of a multiple-exposure study, Bogdanffy et al. [1997] reported a LOAEL of 1000 ppm for histopathologically observed degeneration, necrosis and exfoliation of olfactory epithelial cells of rats exposed to vinyl acetate for 6 hours. Effects were reported to be reversible. No information was provided on clinical signs. Dudek et al. [1996] reported an RD_{50} (concentration estimated to result in a 50% depression in breathing rate) in mice of 380 ppm.

Table A.3.1 provides a summary of the critical lethal concentration data for vinyl acetate in four species. In addition, the table provides 30 minute (0.5-hour) equivalent LC values extrapolated from the original 4-hour LC_{50} values reported in Smyth and Carpenter [1973] using the time scaling methodology outlined in Section 3.5: Time Scaling.

Table A.3.1: Acute Toxicity Data and 30-minute Equivalent Lethal Concentration Values for Vinyl Acetate

Species	Reference	LC_{50} (ppm)	LC_{LO} (ppm)	Time (minutes)	Adjusted 30 minute (0.5-hour) LC*
Mouse	Smyth and Carpenter [1973]	1460	--	240	2920
Rabbit	Smyth and Carpenter [1973]	2760	--	240	5520
Rat	Rousmiantsey et al. [1981]	3238	--	240	6476
Rat	Smyth and Carpenter [1973]	3680	--	240	7360
Guinea Pig	Smyth and Carpenter [1973]	5210	--	240	10420

LC_{50}: The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; LC_{lo}: The lowest lethal concentration of a substance in the air reported to cause death, usually to a small percentage of the test animals; ppm = part per million

*For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (Cn x t = k); no empirically estimated n values were available, therefore the default values were used, n = 3 for exposures greater than 30 minutes and n = 1 for exposures less than 30 minutes.

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Table A.3.2 provides the derivation of multiple 30 minute (0.5-hour) equivalent values that may serve as the final IDLH value for vinyl acetate. The derived values are calculated by dividing the adjusted 0.5-hour LC by the UF selected based on Chapter 4.0: Use of Uncertainty Factors of this CIB. For the assessed for vinyl acetate, the UF of 30 was selected based on (*1*) the extrapolation from a concentration that is lethal to animals, (*2*) animal to human differences, and (*3*) human variability.

Table A.3.2: Calculation of 30 minute (0.5-hour) Derived Values for Vinyl Acetate

Species	Reference	LC_{50} (ppm)	Time (minutes)	Adjusted 30 minute (0.5-hour) LC*	UF†	30 minute (0.5-hour) Derived Value (ppm)§
Mouse	Smyth and Carpenter [1973]	1460	240	2920	30	97.33
Rabbit	Smyth and Carpenter [1973]	2760	240	5520	30	184.00
Rat	Smyth and Carpenter [1973]	3680	240	7360	30	245.33
Guinea Pig	Smyth and Carpenter [1973]	5210	240	10420	30	347.33

LC_{50}: The statistically determined median concentration of a substance in the air that is estimated to cause death in 50% (one half) of the test animals; ppm = part per million; UF = uncertainty factor

*For exposures other than 30 minutes the ten Berge et al. [1986] relationship is used for duration adjustment (Cn x t = k); no empirically estimated n values were available, therefore the default values were used, n = 3 for exposures greater than 30 minutes and n = 1 for exposures less than 30 minutes.

†The selection of the UF for vinyl acetate was based on *Chapter 4.0: Use of Uncertainty Factors.* The UF of 30 was selected based on (1) the extrapolation from a concentration that is lethal to animals, (2) animal to human differences, and (3) human variability.

§Derived values are calculated by dividing the Adjusted 0.5-hr LC by the UF

A.3.2 Human data

No data on lethality in humans from exposure to VA were identified. VA is an eye and throat irritant. Smyth and Carpenter [1973] evaluated the irritating potential at concentrations of 4 ppm, 34 ppm, and 72 ppm, for durations of 2, 120, and 30 minutes, respectively. The 4 ppm

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concentration caused minimal eye, nose and throat irritation, with throat irritation becoming more persistent at 34 ppm. At a concentration of 72 ppm, the subjects reported eye irritation and slight throat irritation, both persisting for up to an hour after exposure. The subjects expressed an unwillingness to work an 8 hour work day at 72 ppm, due to the irritant effects [Smyth and Carpenter 1973]. Dees and Joyner [1969] asked subjects to report symptoms during a 10 minute air sampling under occupational conditions; exposure may have also occurred prior to the sampling, and so the exposure duration is unknown. At 21.6 ppm, eye irritation was described as "intolerable" by all three subjects, and was accompanied by upper respiratory irritation, as indicated by hoarseness and/or cough. No or slight eye irritation was reported at lower levels (9.9 ppm or less). This study is not appropriate as the basis for an IDLH value due to the uncertainties about exposure duration. Hellman and Small [1974] reported an odor detection threshold of 0.12 ppm.

A.4 IDLH Value Rationale Summary

In the absence of adequate human data, the lowest LC_{50} of 1460 ppm for a 4-hour exposure in mice [Smyth and Carpenter 1973] was used to derive an IDLH value. The LC_{50} was adjusted to a 30 minute (0.5-hour) equivalent LC of 2920 ppm. An uncertainty factor of 30 was applied to account for extrapolation from a concentration that is lethal to animals, animal to human differences and human variability, resulting in an IDLH value of 97 ppm (rounded to 100 ppm). This value is supported by animal and human data. For example, Smyth and Carpenter [1973] reported slight throat and eye irritation in workers exposed to 72 ppm vinyl acetate for 30 minutes. Although irritation was not classified as severe, the discomfort produced by this exposure was described as intolerable for an 8 hour work day, but is not expected to be escape impairing or life threatening.

Appendix A References

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Appendix B - IDLH Value Development Prioritization

This appendix identifies how NIOSH will determine the priorities for developing IDLH values. The guidance values play an important role in planning work practices surrounding potential high exposure environments in the workplace and in guiding actions by emergency response personnel during unplanned exposure events. Ideally, IDLH values would be available for all chemicals that might be present under high exposure situations. However, this breadth of coverage of IDLH values is not practical and might not even be necessary for many chemicals, such as those with very low exposure potential or those that are not acutely toxic. In addition, absence of data and limited resources make it difficult to evaluate the multitude of chemicals currently available in commerce. Therefore, a prioritization process is used by NIOSH to ensure that resources are allocated to yield the greatest impact on risk reduction in the event that control measures fail (including respiratory protection devices). This process takes into account both toxicity and exposure potential, and is applied to a broad pool of relevant chemicals (e.g., chemical warfare agents, industrial chemicals, high production volume (HPV) chemicals, or agrochemicals subject to emergency or uncontrolled releases). A qualitative algorithm is used to generate a tentative relative priority ranking. This process is intended only to provide tentative guidance based on a simple approach that uses readily available sources of information. The resulting priorities are further modified based on current NIOSH emphasis areas. For example, chemicals can be added or removed from the list based on new information related to toxicity or exposure potential. The development and use of a documented prioritization process allows for frequent updating of both input data and prioritization criteria to meet changing needs.

Substances considered in the ranking process are compiled from existing databases of chemicals identified by other agencies as “of concern” due to use in chemical terrorism or as chemicals with the potential for exposure due to other uncontrolled releases (and thus have greater opportunities for high acute exposures). Existing lists of agents of concern may not be fully representative of industrial chemicals for which acute exposures may occur during planned activities (e.g., special maintenance activities) or unplanned release events. However, IDLH

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values for many of these sorts of chemicals were included in the original IDLH value development process and in the 1994 updates. Moreover, NIOSH adds additional chemicals of interest that are nominated by interested stakeholders or the subject of new emphasis programs. Chemicals from the following databases (as supplemented by NIOSH chemicals of interest) were included in the current ranking process:

- Hazardous Substances Emergency Events Surveillance (HSEES) – this database contains self-reported incidents of accidental chemical releases. The database was created by the Agency for Toxic Substances and Disease Registry (ATSDR) [ATSDR 2008].

- Emergency Preparedness and Response – a list of specific agents and other threat agents created by the Centers for Disease Control and Prevention (CDC) [CDC 2008].

- Emergency Response Guidebook (ERG) – a list of toxic by inhalation (TIH) chemicals and water-reactive TIH chemicals created by the DOT [US DOT 2008].

- Chemical Facility Anti-Terrorism Standards (CFATS), Appendix A – chemicals of interest to national security created by the Department of Homeland Security (DHS) [US DHS 2007].

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Exposure-related parameters can be divided into two categories: 1) those that provide a direct indication of exposure potential (e.g., number of recorded accidents or spills involving a chemical) and 2) data that provide indirect indication of exposure potential (e.g., volume produced). In weighing such metrics, a balance needs to be struck between the greater confidence provided by direct release data based on the obvious relevance to exposure potential, and the need to have data on exposure potential that are available for most chemicals. Information on direct exposure indicators was obtained from the HSEES database [ATSDR, 2008]. Although only 14 states participate in the program, the data are useful as an exposure indicator. Evidence of frequent past incidents involving uncontrolled releases receive a score of 1 and the absence of reporting of prior releases is scored 0.

Chemical production volume is used as an indirect indication of exposure potential [USEPA 2008]. The USEPA classifies HPV chemicals as those chemicals produced or imported in the United States in quantities of 1 million pounds or more per year; medium production chemicals are quantities of 25,000 to less than 1 million pounds per year, and low production chemicals are quantities less than 25,000 pounds per year. HPV chemicals receive a score of 1, while low and medium production volume chemicals received a score of 0.

Because the aim of the prioritization process is the development of guidance for protection from acute inhalation exposures, endpoints that best inform the potential for life-threatening, irreversible, or escape-impairing effects following acute inhalation exposures receive the greatest weight. The following approach and resources are used to score toxicity considerations:

1. Direct indication of exposure potential (e.g., number of recorded accidents or spills involving a chemical).
    - Evidence of frequent past incidents involving uncontrolled releases.
    - HSEES - collects and analyzes actual hazardous chemical releases and emergency responder injuries.

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- Chemicals with uncontrolled releases [UR] are scored a 1 and lack of reported data is scored a 0.

2. Indirect indication of exposure potential (e.g., volume produced).
   - Indicative of the potential for exposure from the amount of chemical that is produced.
   - USEPA classifies chemicals as low, medium or high production volume.
   - Chemicals classified as HPV are scored a 1, while low and medium volume chemicals are scored a 0.
3. Short term exposure limits [STEL] – NIOSH RELs, OSHA PELs, AIHA WEELs, and ACGIH TLVs [ACGIH 2008; AIHA 2008; NIOSH 2007].

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- STEL values below 20 ppm for vapors and gases or 2 mg/m^3 for particulates provide a reasonable cut point for identifying the most significantly acutely toxic substances.

- Substances with a STEL below these cut points receive a score of 1, while substances with a STEL equal to or greater than these values or that have no available STEL receive a score of 0.

4. Irritant Potential [IRR] – NIOSH Pocket Guide to Chemical Hazards [NIOSH 2007] or the European Union (EU) Risk Phrases (R-phrases) [EU 2008] for irritation.

   - Irritants receive a score of 0.5 and corrosive chemicals receive a score of 1; all other chemicals receive a score of 0.

5. Acute Toxicity [AT] [e.g., Lethal concentration resulting in 50% mortality in the exposed animals (LC_{50})] – Registry of Toxic Effects of Chemical Substances (RTECS) [RTECS 2008]

   - Chemicals classified as extremely or highly hazardous in RTECS or with an EU R-phrase of “very toxic” or “toxic” are scored 1; otherwise, chemicals are scored 0.

   - Chemicals that have not been evaluated using these systems are judged based on the lowest reliable LC_{50} compared to the EU R-phrase criteria.

6. Developmental Toxicant [DT] – NIOSH Pocket Guide to Chemical Hazards [NIOSH 2007] or California Environmental Protection Agency (Cal/EPA) Proposition 65 list [Cal/EPA 2008].

   - Chemicals identified as reproductive/developmental toxicants are scored 0.5; otherwise, chemicals are scored 0.

7. Carcinogenicity [CA] –EPA, International Agency for Research on Cancer (IARC) [IARC 2008], ACGIH [2008], NIOSH Pocket Guide to Chemical Hazards [NIOSH 2007], Cal/EPA Proposition 65 List [Cal/EPA 2008], or other sources.

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- Chemicals classified by recognized systems as probable, likely or known human carcinogens are scored 0.5; otherwise, chemicals are scored 0.

8. Other considerations are used qualitatively to further refine priorities among chemicals with the same risk-based score. These Tier II considerations include:

- Availability of other acute exposure guidance – such guidance includes existing IDLH, AEGL, or ERPG values. The availability of such guidance decreases the urgency for developing (or revising) IDLH values. Availability of toxicity data – the absence of adequate data precludes the development on an IDLH value. The lack of toxicity data for a chemical with high exposure potential is used to identify research needs.
- Availability of exposure monitoring methods – the availability of a validated sampling and analytical method increases the likely near-term utility of a derived IDLH value. The absence of a validated sampling and analytical method for high priority chemicals could be used to identify research needs.
- Presence on existing lists of high priority agents – if other agencies have listed the material as a high priority, then the IDLH value may be useful to other agencies. This type of leveraging of resources is desirable and also helps to harmonize levels of worker health protection among agencies with related missions.
- Degree of safety hazard – if potential risk based on the basis of chemical toxicity is equal, then agents that have a greater degree of safety-related risk (e.g., flammability) are given greater weight. This consideration allows for easier comparison of overall risk profiles and selection of the most appropriate basis for risk management (e.g., developing entry criteria or emergency plans on the basis of whichever is the greater concern safety of chemical health risk).

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The overall priority score is the sum of the exposure score and toxicity score:

- Tier I: Risk Priority Score = Exposure Score [ranges from 0 to 2] + Toxicity Score [ranges from 0 to 3]

$$\textit{Risk Priority Score} = [UR + PV] + [STEL + IRR + AT + DT + CA]$$

Where:

AT = acute toxicant
CA = carcinogenicity
DT = developmental toxicant
IRR = irritant
PV = production volume
STEL = short term exposure limit
UR = uncontrolled releases

- Tier II – Used qualitatively to make an overall judgment on priorities among chemicals with the same risk priority score.

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Appendix C - Critical Effect Determination for IDLH Value Development – Consideration of Severity, Reversibility, and Impact on Escape Impairment

As discussed in the main document, the intent of the IDLH value is to protect against exposures that are “likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." In other words, the most appropriate effects to use as the basis of the IDLH value derivation are those that are severe, irreversible, or escape-impairing. Scientific judgment is an important aspect in evaluating severity of effects and determining which ones are irreversible, but guidance is available from a number of different sources.

Severe adverse effects that are not necessarily immediately escape impairing are judged on a case-by-case basis weighing considerations, including the need for medical treatment, the potential for altered function or disability and the potential for long-term deficits in function. These include severe, but reversible, acute effects such as hemolysis, chemical asphyxia, delayed pulmonary edema, or significant acute organ damage (hepatitis, decreased kidney function, etc.). If these effects could be caused by the chemical, it is important that the available toxicity studies evaluated the development of such effects by, for example, allowing sufficient time between exposure and evaluation of the endpoint.

Guidance on evaluating and ranking the severity of toxic effects is available from a number of organizations. DeRosa et al. [1985] developed a 10-category scheme for evaluating noncancer toxicity in the evaluation of Reportable Quantities under the USEPA Superfund legislation. Although designed for the context of chronic exposures, this approach provides insight into the relative severity of different types of histopathology and developmental toxicity. The Agency

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for Toxic Substances and Disease Registry (ATSDR) includes the following five severity rankings [Pohl and Abadin 1995]:

- No Observed Effect Level (NOEL)
- No Observed Adverse Effect Level (NOAEL)
- Minimal Lowest Observed Adverse Effect Level ($LOAEL_1$)
- Moderate Lowest Observed Adverse Effect Level ($LOAEL_2$)
- Frank Effect Level (FEL)

ATSDR applies this approach from acute exposures (defined as exposures up to 14 days) through chronic exposures, and a number of publications are available on applying this approach to various types of effects [e.g., Abadin et al. 1998, 2007; Chou and Pohl 2005; Pohl and Chou 2005; Pohl et al. 2005]. Although intended for a different purpose, these analyses can provide insights into the evaluation of effect severity. In particular, the "moderate" LOAEL category used by ATSDR is more likely to be considered severe or irreversible, and thus relevant to IDLH value development. Guidance on evaluation of the severity of effects is also available from USEPA's RfC guidelines [USEPA 1994] and from the American Thoracic Society [e.g., Pellegrino et al. 2005].

Determining which effects are escape-impairing is complicated both by the limited guidance available from other sources and by the fact that reporting of signs and symptoms for similar underlying effects may differ across human and animal studies. For example, the same underlying mechanism may be described as inducing intolerable irritation in a human clinical study or case report, but may manifest as changes in respiration rate, nasal discharge or altered activity level in an acute toxicity test in animals. For this reason, guidance was developed that allows for more consistent assigning of comparative severity of observed effects (i.e., escape impairing versus non-escape impairing) for commonly observed adverse effects used as the basis of IDLH values. Table C.1 provides guidance for classification of many effects commonly seen in acute studies. Due to the nature of the evaluation methods, endpoints that can be evaluated in

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humans are generally limited to clinical signs and symptoms, along with some specialized testing, and some histopathology evaluation that can be conducted non-invasively (e.g., for the nasal cavity), or can be inferred from other evaluations (e.g., pulmonary edema).

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Table C.1: Common Clinical Signs, Symptoms and Histopathological Abnormalities Observed During Acute Exposures[11]

Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Irritation - Ocular				
Signs and Symptoms -Ocular				
Eye irritation (subjective description)	Yes	☒	☐	If moderate or severe
Lacrimation (excessive tearing, clear or colored)	Yes	☒	☒	If severe (assumes will be accompanied by other severe irritation responses)
Blepharospasm (eye squinting and shutting)	Yes	☒	☒	If severe
Reduced/poor vision	Yes	☒	☐	If severe
Mouth- or face-pawing activity	No	☐	☒	May be observed even during mild irritation
Eye blink rate/frequency	No	☒	☒	Difficult to use as a correlate of irritation, although some investigators assert that it may be useful as a marker of moderate to severe eye irritation

[11] Checked box indicates effect is observed in the species

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Ocular Examination Findings				
Swelling of eyelids	Yes	☒	☒	If eyelids are closed (more than half-closed)
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	No	☒	☒	Assuming no significant impairment of vision
Easily discernible translucent area, details of iris slightly obscured	No	☒	☒	
Nacreous (lustrous) area, no details or iris visible, size of pupil barely discernible	Yes	☒	☒	
Opaque cornea, iris not discernible through the opacity	Yes	☒	☒	If severe, assumes will significantly impair vision

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Markedly deepened rugae (folds or wrinkles), congestion, swelling, moderate circumcorneal hyperemia, or injection, or any of these or combination of any thereof, iris still reacting to light (sluggish reaction is positive)	Yes	☒	☒	
No reaction to light, hemorrhage, gross destruction (any or all of these)	Yes	☒	☒	
Ocular hyperemia (blood vessels hyperemic causing red eye)	No	☒	☒	
Cornea, inflammation or abrasion	Yes	☒	☒	
Cataract	Yes	☒	☒	
Inflammation of the eyes	Yes	☒	☒	If inflammation severe, assumes this correlates to severe irritation; large changes in some sensitive biomarkers may not necessarily indicate severe irritation responses.

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Irritation - Respiratory				
Nasal Signs and Symptoms				
Nasal irritation or pain (subjective description)	No	☒	☐	
Nasal localization	No	☒	☐	Endpoint differentiates sharp smell from irritation
Sneezing	Yes	☒	☒	If severe
Nasal congestion	No	☒	☒	
Nostril discharges: red or colorless	No	☒	☒	
Thickness/swelling of nasal mucosa (decreased nasal cross-sectional area)	No	☒	☒	Methods measuring mucosal thickness not directly related to sensory irritation effects
Increased Nasal airway resistance	No	☒	☐	
Respiratory Tract Symptoms				
Dry cough	Yes	☒	☐	If severe
Cough with mucus or blood	Yes	☒	☐	If severe
Chest wheezing	Yes	☒	☐	If severe, assumes may impair breathing

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Rales (rapid series of short loud sounds)	No	☒	☐	
Breathing Rate/Volume measured by PFT results)	Yes	☒	☒	If severe in humans assumes may impair breathing; concentrations in the range of the RD_{50} in rodents
Dyspnea (difficult or labored breathing observed as abdominal breathing or gasping)	Yes	☒	☐	If severe in humans assumes may impair breathing
Painful breathing	Yes	☒	☐	If severe in humans, assumes sufficient to impair breathing
Apnea (a transient cessation of breathing following a forced respiration)	Yes	☒	☒	Indication of sufficient irritation to modify breathing
Tachypnea (quick and usually shallow respiration)	Yes	☒	☒	Indication of sufficient irritation to modify breathing
Cyanosis (bluish appearance of tail, mouth, foot pads, skin or mucous membranes)	Yes	☒	☒	If severe, assumes sufficient to impair respiration
Laryngoconstriction	Yes	☒	☒	If severe, assumes may impair breathing
Bronchoconstriction	Yes	☒	☒	If moderate or severe, assumes may impair

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
				breathing
Respiratory Tract Histopathology				
Nasopharynx inflammation	No	☒	☒	
Nasopharynx erosion or necrosis	No	☒	☒	
Larynx inflammation	No	☒	☒	If severe, assumes may impair breathing
Larynx erosion or necrosis	Yes	☐	☒	If moderate or severe, assumes may impair breathing
Tracheal or bronchial inflammation	Yes	☐	☒	If severe, assumes may impair breathing
Tracheal or bronchial erosion or necrosis	Yes	☐	☒	If moderate or severe, assumes may impair breathing
Alveolar hemorrhage or necrosis	Yes	☐	☒	If observed, assumes may impair breathing
Pulmonary edema	Yes	☒	☒	If observed, assumes may impair breathing
Neurological				
Signs and Symptoms				

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Arousal state	No	☒	☒	If sluggish with some exploratory movements with periods of immobility, or hyperalert, excited, sudden bouts of running or body movements, or changes in rearing
Headache	Yes	☒	☐	Only if described in study as debilitating
Lightheadedness, dizziness/faintness	Yes	☒	☐	If moderate or severe
Lassitude/lethargy (feeling low in energy or slowed)	No	☒	☐	Assume if severe, lassitude would be seen as extreme drowsiness/fatigue
Extreme drowsiness, fatigue or sleepiness (somnolence)	Yes	☒	☐	If severe
Narcosis (stupor)	Yes	☒	☒	If observed
Frank effects (including postural observations – excessive sway, lying on side, limbs in the air, loss of balance -, stupor, convulsions, seizure, coma)	Yes	☒	☒	If observed
Exhilaration (unusual)	No	☒	☐	
Euphoria (a feeling of exaggerated elation)	No	☒	☐	

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Loss of concentration	Yes	☒	☒	If severe
Loss of recent memory	No	☒	☒	
Long-term memory loss	No	☒	☒	
Unstable moods	No	☒	☐	
CNS excitability				
Clonic movements (marked by alternate contraction and relaxation of muscles)	Yes	☒	☒	If moderate-severe body tremors and myoclonic jerks
Tonic movements (marked by continuous muscular contractions)	Yes	☒	☒	If head and body rigidly forward or backward
Autonomic effects				
Palpebral closure, ptosis or relaxation of nictating membranes	Yes	☒	☒	If eyelids or nictating membranes drooping; drooping of nictating membranes would not be observed in humans
Urination	Yes	☒	☒	Common effects of nerve agents and accompanied by changes that impair escape

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Defecation	Yes	☒	☒	Common effects of nerve agents and accompanied by changes that impair escape

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Piloerection (contraction of erectile tissue of hair follicles resulting in rough fur)	No	☐	☒	
Hypo- or hyperthermia	Yes	☒	☒	If severe
Excessive perspiration/sweating/panting	No	☒	☒	Common effects of nerve agents and accompanied by changes that impair escape
Salivation	No	☒	☒	Common effects of nerve agents and accompanied by changes that impair escape
Syncope (loss of consciousness)	Yes	☒	☒	If observed
Blurred vision	Yes	☒	☐	If severe
Mydriasis (reflex pupillary dilation)	Yes	☒	☒	If severe
Miosis (constriction of pupil, regardless of light)	Yes	☒	☒	If severe
Ptosis (drooping of upper eyelids)	Yes	☒	☒	
Chromodacryorrhea (red lacrimation)	No	☐	☒	
Loss of libido	No	☐	☒	

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Muscle tone/equilibrium				
Abnormal gait or postural observations	Yes	☒	☒	If sufficient to impair balance or locomotion
Mobility	Yes	☒	☒	If severely impaired
Righting	Yes	☐	☒	If moderately or severely impaired
Forelimb grip strength	Yes	☐	☒	If severely impaired
Landing foot splay	Yes	☐	☒	If significantly increased a measure of postural instability
Fasciculation (muscular twitching)	Yes	☒	☐	If severe
Muscle weakness of extremities (foot drop)	Yes	☒	☐	If severe
Decreased manual dexterity	Yes	☒	☐	If severe
Decreased nerve conduction velocity	Yes	☒	☐	If accompanied by changes that affect locomotion
Sensorimotor reactivity				
Click response	No	☐	☒	Sensitive response
Touch response	No	☐	☒	Sensitive response
Tail pinch response	Yes	☐	☒	If no or limited reaction indicates decreased

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
				sensory ability and CNS impairment
Paresthesia (numbness/tingling body parts)	Yes	☒	☐	If impairs locomotion or ability to grasp
Perception speed	No	☒	☒	Sensitive response
Reaction time (simple or choice)	No	☒	☒	Sensitive response
Auditory vigilance	No	☒	☒	Sensitive response
Visual time discrimination	No	☒	☒	Sensitive response
Depth and form perception	No	☒	☒	Sensitive response
Tinnitus (ear ringing)	No	☒	☐	
Pressure in the ears	No	☒	☐	
Reduced hearing acuity	No	☒	☐	
Insomnia or wake frequently	No	☒	☒	
Nervous System Histopathology				
Central nervous system lesions	Yes	☐	☒	If degenerative change observed
Peripheral nervous system lesions	Yes	☐	☒	If degenerative change observed

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Other				
GI Tract Signs and Symptoms				
Stomachache	Yes	☒	☐	If severe – e.g., causes involuntary doubling over
Nausea	No	☒	☐	May be accompanied by weakness or dizziness that will be considered escape-impairing
Diarrhea	No	☒	☐	
Vomiting	Yes	☒	☒	If severe
Cardiovascular Changes				
Change in blood pressure	Yes	☒	☒	If severe, assumes may induce faintness or dizziness (extreme hypotension)
Changes in heart rate (tachycardia or bradycardia)	Yes	☒	☒	If severe or accompanied by other impairing cardiovascular change
Tightness in the chest	Yes	☒	☐	If severe or accompanied by other impairing cardiovascular change
Pains in heart or chest	Yes	☒	☐	If severe or accompanied by other impairing cardiovascular change

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Clinical Sign(s)	Escape-impairing?	Humans	Animals	Comments
Arrhythmias	Yes	☒	☒	Assumes sufficient to impair systemic blood flow
Ventricular fibrillation	Yes	☒	☐	If observed

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Appendix C References

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Appendix D-Analyses Supporting the Development of Uncertainty Factor Approach

To derive a scientifically-based approach for the use of UFs in the derivation of IDLH values, several analyses were conducted to determine the appropriate size of the UF for extrapolating from various points of departure, taking into account the weight-of-evidence approach and MOA considerations described above. Two approaches were used. Approach One involved a detailed evaluation of acute toxicity data for a selection of 20 chemicals, while Approach Two evaluated the MOAs identified from a larger dataset of 94 chemicals.

For Approach One, 20 case-study compounds with high-quality animal lethality studies and adequate human effects data to estimate lethality thresholds were identified. The Log-Probit model of USEPA's BMDS was used to calculate the LC_{50} and LC_{01} values based on the mortality incidence data for each of the animal studies of adequate quality. All of the animal LC_{50} values and human lethality threshold data were adjusted to 30-minute equivalent values using the method of ten Berge and colleagues [ten Berge et al. 1986] using chemical-specific values of "n" for lethality whenever possible, and using an "n" of 1 for time correction of human effects other than lethality (e.g., irritation or signs of CNS depression), since the correct approach for extrapolation is uncertain for less-than-lethal effects. Adequate quantitative data are rarely available for severe adverse effects in humans to support concentration-response modeling. In particular, thresholds for lethality are difficult to estimate from the very limited available case report information. However, available effect levels in humans gleaned from peer-reviewed secondary sources were arrayed by concentration (Conc), duration of exposure (time, t), the concentration x duration product (Conc × t = k) and severity of effect for each study that provided human response data

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Results of this analysis are shown in Table D.1. The analysis found that animal lethal concentrations and human effect thresholds were generally correlated for this limited dataset. Additional analyses were conducted by MOA category (e.g., irritant, CNS depressant, or "other"). Group means for each MOA category were not significantly different when comparing animal lethal concentrations (LC_{50} and LC_{01}) to human lethality thresholds (human LC_{LO} values). However, group means for the three MOA categories did differ significantly for the ratios of animal lethal concentrations (LC_{50} and LC_{01}) versus the human LOELs for the 20 case-study chemicals. The mean LC_{50}/human LOEL ratio was greatest for irritants, followed by chemicals that induce CNS effects, and then chemicals that had other MOAs.

As shown below in Table D.1, comparison of animal RD_{50} values to current IDLH values suggests that, on average, the RD_{50} corresponds to a human severe irritation threshold, since the IDLH values used in the analysis were based on irritant effects in humans. This interpretation is consistent with the results of [Schaper 1993] that suggested that exposure at the RD_{50} would likely cause intolerable sensory irritation. However, it is noteworthy that the RD_{50} would have been considered in the overall weight of evidence in setting the IDLH values used in our analysis, which might have biased the results towards a value of 1.

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Table D.1: Ratio of lethal concentrations from animal studies and observed or estimated human effect levels

Comparison	Median	95th Percentile
LC_{50}/LOEL*	25	330
LC_{01}/LOEL	15	130
LC_{50}/LC_{LO}	2	13
LC_{01}/LC_{LO}	1.5	11
LC_{50}/IDLH value†	8	67
$RD^{‡}_{50}$/IDLH value†	1	9

*Based on analysis of 20 case study substances. The numerator is the value from animal studies and the denominator is the human effect level or value of the current IDLH value.

†Based on analysis of current IDLH values.

‡RD = Respiratory depression

The second approach used data directly from current IDLH value documentation to analyze all of the chemicals in the current list of IDLH values that are based on human effects data and had at least one reported LC_{50} value resulting in a list of 94 chemicals for further examination. For each of these chemicals, the analysis identified the value of the lowest adequate 30-minute adjusted LC_{50} value, the current IDLH value, and the MOA for which the current IDLH value was set. As for the first approach, three MOA categories were used:

1. Irritation,
2. Neurological effects, and

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3. "Other."

It was noted that the "other" category included several pesticides that act via inhibition of cholinesterase. Although this group was not analyzed separately, it does form a potential fourth group for additional analysis. The cholinesterase inhibitors were not included in the general neurological effects category, since they have a specific underlying mechanism that might yield significant differences in lethality to non-lethal effect ratios as compared to other organics that act via the more general mechanisms of CNS depression. Published data were also used to compile RD_{50} estimates (the concentration of the chemical that results in a 50% decrease in respiratory rate in a standardized rodent test) for these same chemicals.

The distribution of the LC_{50}/IDLH value ratios is shown in Figure D.1. Results of the LC_{50}/IDLH value ratio analysis (shown in Figure D.1) indicate that a factor of 10 would account for human effect thresholds for effects such as severe irritation and neurological effects, for approximately half of the chemicals reviewed, although a factor as high as 100 may be needed to cover 95% of chemicals. Distribution of RD_{50}/IDLH value ratios for 26 chemicals yielded a median ratio of 1, suggesting that exposure at the RD_{50} would generally result in sensory irritation of sufficient severity to be judged as escape-impairing. This interpretation is consistent with the results of [Schaper 1993] that suggested that exposure at the RD_{50} would likely cause intolerable sensory irritation. Overall, no clear pattern regarding MOA was evident when comparing LC_{50}/IDLH value ratios and its primary MOA for the 94 chemicals or comparing RD_{50}/IDLH value ratios for the 26 chemicals.

This analysis hypothesized that potent irritants may have a greater difference between the LC_{50} and the threshold for serious effects in humans as compared to chemicals that cause toxicity via other modes of action. If this hypothesis was true, then the implication would be that deriving an IDLH value from an LC_{50} for such chemicals would require a greater

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UF than would be needed for chemicals with other modes of action. The analysis produced mixed results with a significant MOA effect observed for a subset of 20 chemicals, but not in a broader analysis of current IDLH values. Based on these results, the data are not adequate to recommend different UF by MOA category.

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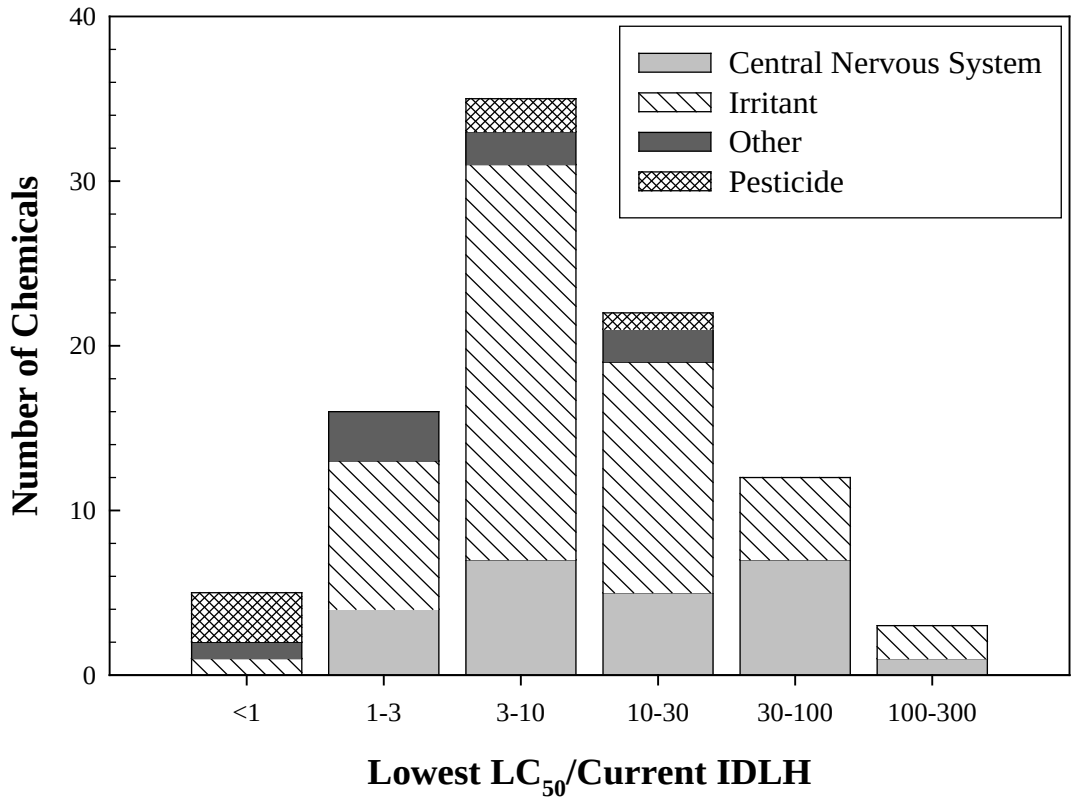
Figure D.1: The distribution of ratios of the lowest 30-minute adjusted LC_{50} value to the current IDLH value is shown for 94 substances representing four MOA categories to evaluate the potential uncertainty value that provides adequate coverage for each MOA.



LC_{50} – Concentration to cause a 50% mortality rate in an acute toxicity study.

Irritants – The critical effect that would be the basis for an IDLH value is irritation.

CNS Depressants – The critical effect that would be the basis for an IDLH value is CNS system depression.

Other – The critical effect that would be the basis for an IDLH value arises from a MOA other than irritation or CNS depression.

Pesticide – The critical effect that would be the basis for an IDLH value is cholinesterase inhibition.

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Appendix D References

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