Attachment F: NIOSH Response to Summarized Stakeholders' (Public) Comments

NIOSH Current Intelligence Bulletin (CIB): Derivation of Immediately Dangerous to Life or Health (IDLH) Values
Prepublication Package for NIOSH OD Review
July 1, 2013

1.0 Background

The *NIOSH Current Intelligence Bulletin (CIB) – Derivation of Immediately Dangerous to Life or Health (IDLH) Values* was developed to update the scientific rationale for deriving IDLH values. The finalized CIB supersedes previous NIOSH policy on the derivation of IDLH values. The NIOSH policy and resulting IDLH methodology were last updated in 1994 [NIOSH 1994][1].

The intended audience for the CIB includes other government agency science and policy experts, occupational safety and health professionals, in addition to emergency preparedness and planning managers. The document provides this professional audience with the current recommendations used by NIOSH for developing IDLH values based on modern principles and understanding of human health risk assessment methods. The methodology presented in the CIB considered the methods used for related risk assessment efforts in the Federal Government and evaluation of the available scientific literature relevant to setting inhalation-based acute exposure guidelines for protection of human health in the fields of toxicology and occupational health.

2.0 Description of Public and Stakeholder Review

On January 24, 2011, NIOSH announced in the Federal Register [76 Fed. Reg. No. 15 (2011); 4115-4116] the availability of the draft IDLH CIB for stakeholder and public review. During the 90 day review period that closed in April 2011, six submissions from the public and stakeholders were received by the NIOSH Docket Office for the IDLH CIB, NIOSH Docket #156. The names and affiliations of the stakeholder reviewers are as follows:

1. Army Institute of Public Health (AIPH; formerly US Army Center for Health Promotion and Preventive Medicine), US Army Public Health Command, Aberdeen Proving Grounds, Maryland.
    - Specific comments were submitted by the following AIPH staff: Ms. Rebecca Adams, Mr. Christopher Carroll, M.S.E.S.; Ms. Veronique Hauschild, M.P.H.; Ms. Irene L. Richardson, M.Sc., R.S.; Dr. Laurie Roszell, Ph.D.; and Mr. John J. Resta, M.C.E.
2. Dr. Ernest V. Falke, Ph.D., US Environmental Protection Agency (EPA), Acute Exposure Guideline Levels Program, Washington, District of Columbia
3. Mr. William Finegan, Bensalem Emergency Management Service, Bensalem, Pennsylvania
4. Dr. James Holler, Ph.D., Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology and Environmental Medicine, Prevention, Response and Medical Support Branch, Atlanta, Georgia
5. Mr. John S. Morawetz, M.Sc., ICWUC Center for Worker Health & Safety Education, Cincinnati, Ohio

[1] All citations included within this document can be located with the *NIOSH Current Intelligence Bulletin (CIB) – Derivation of Immediately Dangerous to Life or Health (IDLH) Values.*

6. Dr. George Rusch, Ph.D., DABT, ATS, Risk Assessment and Toxicology Services, Bridgewater, New Jersey

No comments were received from the public.

All comments submitted by stakeholders were synthesized to provide a collective response to similar topics. The topics were grouped into one of the following categories:

1. Nature and Form of Exposure
2. Route-to-Route Extrapolation
3. Safety Issues [Lower Explosive Limits (LEL)]
4. Uncertainty Factors (UFs)
5. Chemical Mixtures and Other Stressors
6. Relationship Between the IDLH Values and Acute Exposure Guideline Levels (AEGLs)
7. Case Study (Appendix A)
8. Data Quality and Selection
9. Point of Departure (POD) Selection and Weight of Evidence (WOE)
10. Duration Adjustment (Time Scaling)

3.0 Category Summary and NIOSH Response

Category 1 – Nature and Form of Exposure

Stakeholder comments questioned whether the IDLH values could also be used to address non-inhalation exposures (i.e., skin contact). The primary issue cited was the need for exposure recommendations that would aid in identifying IDLH conditions that arise from skin contact with chemicals. The stakeholder requested that NIOSH develop "dermal" IDLH values to serve as complementary recommendations.

NIOSH Response: NIOSH has added supplemental language throughout the Current Intelligence Bulletin (CIB), including the Executive Summary and Chapter 1 that clarifies the role of IDLH values. As indicated in the CIB the IDLH values focus on the characterization of airborne concentrations of chemicals capable of causing escape-impairing effects, irreversible effects, or death following short durations (<30 minutes). The IDLH values may indirectly incorporate considerations of potential multiple-route exposure, where dermal exposures arise from deposition of airborne chemicals or absorption of vapor phase chemicals through the skin. However, the IDLH values are not intended as dermal exposure guidelines.

Although NIOSH acknowledges that direct skin contact to certain chemicals may be life-threatening, the development of quantitative "dermal" IDLH values is problematic due to the absence of dermal/surface contact sampling techniques and uncertainty regarding identifying the appropriate exposure metric. For example, should a "dermal" IDLH value be derived based on the quantity of a chemical on the surface of an object, quantity of a chemical on the surface of the skin, quantity of a chemical that penetrates the skin, or quantity of a chemical that was absorbed into the skin and has been distributed systemically?

Validated methods to measure these different exposure or dose metrics would also be needed. This same issue has inhibited the development of quantitative occupational exposure limits (OELs) for dermal contact and is an ongoing research need.

An alternative source of guidance to inform risk management decisions from dermal exposure, including consideration of life-threatening acute skin exposures, is available in a previous NIOSH publication. The NIOSH technical document entitled *CIB 61: A Strategy for Assigning the New NIOSH Skin Notation* [NIOSH 2009-147] is intended to provide a strategy for the assignment of qualitative hazard designations capable of clearly delineating between the various health effects caused by skin contact with chemicals. One of the designations used in the Skin Notation strategy is the SYS [FATAL] notation that denotes chemicals that may cause life-threatening effects following acute dermal exposures. This notation and the Skin Notation CIB provide an alternative resource that in qualitative terms fills the same general objectives as would a "dermal" IDLH value. The notation approach is most consistent with the current state of the science in dermal exposure assessment.

Stakeholders inquired about the impact of physical state of a chemical and the role this consideration has in deriving an IDLH value. More specifically, stakeholders questioned if an IDLH value is derived for a chemical that is a particulate (i.e., solid particle or liquid particle as an aerosol), whether the IDLH documentation for the chemical would recommend a size fraction (e.g., inhalable, thoracic, respirable) that aligns with the expected toxicity.

NIOSH Response: NIOSH agrees with the stakeholder comments that an IDLH value developed for particulate-phase chemicals (solid or liquid aerosol) should provide information relating to the relevant size fraction. Recommendations relating to size fractions for aerosols will be included in the IDLH support documentation for chemicals that have sufficient data to identify which fraction is most relevant to the acute toxicity that serves as the basis for the IDLH value. If such data are not available, NIOSH will note in the IDLH support documentation that the size fraction that represented the greatest hazard could not be determined. In such cases total inhalable particulate is used as the basis for the IDLH value. This approach is consistent with text in the CIB (see Section 3.4.2.3 that notes toxicity may vary for a chemical based on its physical state).

Category 2: Route-to-Route Extrapolation

Stakeholders questioned 1) the use of route-to-route extrapolation techniques in the derivation of IDLH values and 2) the key assumptions for these techniques outlined in the draft CIB. Route-to-route extrapolation is a technique that is applied by most organizations that derive human health risk assessments when data provide sufficient evidence that the toxicological effects associated with a chemical occur independently of exposure route. As part of the 1994 NIOSH IDLH update project, several IDLH values were derived based on toxicity studies that employed oral dosing or intraperitoneal (i.p.) injection. No current IDLH values are based on studies using dermal administration as the dosing route, although this is feasible when absorption kinetics are adequately characterized. Because of uncertainties in route-specific toxicokinetics and toxicodynamics, the use of toxicity data from oral, i.p. or dermal dosing is considered inferior to studies using inhalation exposures.

The stakeholders' first concern related to the use of route-to-route extrapolation techniques during the derivation of IDLH values. The stakeholders stated that these techniques should only be applied when no inhalation data are available to develop an IDLH value for a chemical, and there is an overwhelming need to still establish an IDLH value.

NIOSH Response: NIOSH agrees with the stakeholders' assertions that route-to-route extrapolation should only be applied when no inhalation data are available, but there is a compelling need for the establishment of an IDLH value. Supplemental language (*see Chapter 3*) has been included in the CIB to provide guidance on the use of route-to-route extrapolation when deriving IDLH values. The guidance states, "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 a respiratory tract or eye irritant, or if the chemical is expected to target the route of entry (i.e., respiratory tract) as the most sensitive end point."

The stakeholders' second concern relates to key assumptions used in the route-to-route extrapolation calculations. The specific issue noted relates to the volume of air used to calculate the inhalation equivalent concentration for the systemic dose obtained from studies using dosing via other routes (i.e., conversion of a dose in mg chemical/kg body weight-day to mg chemical/m^3 of air). The 1994 update to the IDLH values used a volume of 10 cubic meter (m^3) to calculate the inhalation equivalent concentration from a systemic toxicity study dose. This value represents the volume of air assumed to be inhaled over the course of a typical 8-hour shift at light work load. The resulting calculated inhalation concentration is health protective, and may result in IDLH values that are more than adequately protective.

In the draft IDLH CIB (see *Section 3.4.2.4*) reviewed by the stakeholders, NIOSH outlines the use of 10 cubic meters (m^3) as the default volume of air. The stakeholders stated that use of this volume of air is inappropriate because the volume of air is too high for a 30-minute exposure, which is the basis of an IDLH value. The stakeholders advocated the use of 1.5 m^3 as the default volume of air intake to be used during route-to-route extrapolation calculations. This volume is based on the assumption that a worker breathes at a rate of 50 liters/minute for 30 minutes, which equals 1.5 m^3. This default assumption has been applied to establish other acute exposure guidelines, including the Acute Exposure Guideline Levels (AEGLs).

NIOSH Response: NIOSH agrees with the stakeholders' assertions and has modified the CIB to use 1.5 m^3 as the default volume of air during the establishment of IDLH values using route-to-route extrapolation techniques in converting systemic doses to an inhalation equivalent concentration. Use of the 1.5 m^3 value as a default is most consistent with the relevant exposure scenarios associated with IDLH conditions. The CIB has been modified (see *Section 3.4.2.4* and *Appendix E*) to provide supplemental information regarding the rationale for the 1.5 m^3 value as the most appropriate assumption for route-to-route extrapolation calculations.

Category 3: Safety Issues [Lower Explosive Limits (LEL)]

The stakeholders expressed concerns about the establishment of IDLH values derived strictly on the basis of health considerations arising from chemical toxicity. The primary concern is the exclusive use of health-based data during the establishment of IDLH values, with the result that safety issues, such as explosive atmospheres, would be overlooked. More specifically, the stakeholders advocated for the use of 10% of the lower explosive limit (LEL) as an alternative default in the CIB. In essence, if 10% of the LEL is lower than the calculated health-based estimates, the IDLH value would be based on the10% LEL estimate.

NIOSH has historically employed the approach of using safety considerations as an alternative basis of an IDLH value and this was done as part of the 1994 IDLH Update Project [NIOSH 1994]. In the 1994 update, it was stated that, "...All 'preliminary' IDLHs derived during this update were checked against the following factors prior to establishing the final "revised" IDLH: Lower explosive limit (LEL): It was decided to restrict the 'routine' entry into a possible explosive atmosphere to concentrations no greater than 10% of the LEL. [Note: SCP-derived IDLHs were set at 100% of the LELs if there were no known serious health hazards below these values. However, OSHA considers concentrations in excess of 10% of the LEL to be a hazardous atmosphere in confined spaces [29 CFR 1910.146(b)].]" This established the practice of settings based on safety issues, instead of health considerations.

NIOSH Response: After reviewing the comments and subject matter more closely, NIOSH has modified the draft CIB to include safety considerations (i.e., explosivity and combustibility) as a primary line of data that will be examined during the establishment of an IDLH value. It is believed that the inclusion of both lines of data (i.e., health and safety considerations) in the derivation of an IDLH value provides occupational health professionals with the information needed to support informed decisions aimed at protecting workers' safety and health. A common consideration requiring evaluation in the derivation of IDLH values is the potential for explosive concentrations of a flammable gas or vapor to be achieved at toxicologically relevant air concentrations. Inclusion of safety considerations into the process for establishing IDLH values is consistent with the historic method used to develop IDLH values prior to the development of the protocol outlined in the draft CIB. For gases and vapors, NIOSH has adopted a threshold of 10% of the LEL as a default basis for the IDLH values based on explosivity concerns. In such events, when the air concentration that corresponds with 10% of the LEL is less than the health-based value using the approach outlined in Chapter 3.0, this air concentration will become the default IDLH value. The following hazard statement will be included in the support documentation: *"The health-based IDLH value is greater than 10% of the LEL (>10% LEL) of the chemical of interest in the air. Safety considerations related to the potential 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.

For dust, the equivalent default approach would be using 10% of the minimum explosive concentration (MEC). However, determining the combustibility of dusts is too complex to assign a single default measure. Dust combustibility and explosivity are dictated by the relationships among substance and scenario-specific factors including (1) particle size distribution, (2) minimum ignition energy, (3) moisture content, (4) explosion intensity and (5) dispersal in air [Cashdollar 2000]. The ability to quantify combustible dust specific concentrations for application of an IDLH is often not possible given the absence of critical chemical-specific data, such as the MEC or the other previously identified factors.

NIOSH will critically assess the explosive nature of a dust when sufficient technical data are available. If determined to be appropriate, the findings of this assessment will be incorporated in the derivation process to ensure that the IDLH value protects against both health and safety hazards. When a dust has been identified as combustible, NIOSH will include the following hazard statement: *"Dust may represent an explosive hazard. Safety considerations related to hazard of explosion must be taken into account."* In addition, the notation **(Combustible Dust)** will appear beside the IDLH value in the NIOSH Pocket Guide to Chemical Hazards [NIOSH 2005] and in other NIOSH publications. Supplemental information on the combustibility of dust can be located on the OSHA Combustible Dust webpage (http://www.osha.gov/dsg/combustibledust/).

Category 4: Uncertainty Factors (UFs)

Some stakeholders recommended that NIOSH use the same approach for assigning UFs as other groups, such as the AEGL committee, which rely on multiplication of individual factors. The review draft of the CIB used an approach for selecting UFs based on identifying typical ranges and preferred defaults for different data scenarios that are adjusted further based on the overall weight of evidence for each chemical on a case-by-case basis. This is a hybrid of approaches used by other organizations that establish acute exposure guidelines and is based on an analysis done specifically for IDLH values (Section *Appendix D*). For example, the AEGL methodology uses a series of default UFs that are multiplied and then adjusted post-hoc based on the reasonableness of the resulting derived value when compared to the data set as a whole. On the other hand, many leading expert groups that establish OELs use a weight of the evidence approach that has no published default UFs or published UF ranges. The NIOSH hybrid approach uses a preferred composite uncertainty as a starting point based on the nature of the overall data set and communicates areas of uncertainty that impacted the final IDLH value in the rationale statement. Stakeholders indicated that additional information on this approach, in addition to the logic behind the individual UFs is needed to better communicate the uncertainty associated with a specific IDLH value.

NIOSH Response: NIOSH has selected a hybrid approach that provides a data-informed starting point for the analysis, supported by empirical analysis (see *Appendix D.2*). The approach is intended to provide flexibility in UF selection by accounting for typical overlaps in individual UFs and data hierarchies at the beginning of the UF selection process. This provides an increase in transparency over the weight of evidence approach, without requiring significant effort to explain departures from rigorous defaults that is often associated with the application of UFs. The NIOSH hybrid approach (Method 2 in *Appendix* D-2) is intended as a reasonable blend of providing transparency in the basis for an assessment, without the rigid application of default values that may require extensive post-hoc explanations. Multiplication of default UFs tends to yield IDLH values that are more than adequately protective or do not align with the totality of the data set – this situation is very common due to the nature of the datasets often available for IDLH derivation. This conclusion is based on experience in developing IDLH values for many chemicals with diverse datasets and further systematic analyses provided in *Appendix* D. In developing the approach, it was considered that setting IDLH values lower than needed, can present additional safety risks in the context of the intended application as a tool for respiratory protection selection.

NIOSH also notes that the robust application of each of various methods if done correctly is expected to yield similar results. This is demonstrated in Appendix A for chlorine. The AEGL-2 value (30 minute) and proposed IDLH value are both 2.8 ppm. Although these estimates are the same concentration, the underlying basis is different. To further test this hypothesis, a correlation analysis was conducted to evaluate the overall relationship between proposed IDLH values developed under the new methodology and current 30-minute AEGL values. The results of this analysis provided evidence of a reasonable correlation between the current IDLH values and the AEGL values. The correlation is best with AEGL-2 values, which was expected based on the similarity of the effect severity of most interest for the IDLH with the AEGL-2 definitions. The general correlation for independently derived IDLH and AEGL values provides support for Method 2 that maintains a clear relationship to the goals and history of the IDLH Program. In comparing the IDLH and AEGL methods regarding the use of UFs, the primary difference is a trade-off between the level of transparency afforded by default UF approaches versus the lack of clarity arising from complex explanations of departures from defaults in a concise IDLH documentation format.

A stakeholder indicated that additional clarification on the multiplication of UF should be included within the CIB. More specifically, the applied uncertainty factors are typically 1, 3, or 10, with 3 actually being 3.16 (the square root of 10). If multiple uncertainty factors are multiplied together, 3 * 3 * 3 actually equals 30 not 27 because we are actually multiplying 3.16 * 3.16 * 3.16. This point is often not intuitive to many people and the stakeholder stated that supplemental details should be included on the topic.

NIOSH Response: NIOSH agrees with the stakeholder's comment that this issue may not be intuitive for people with limited experience in the area of quantitative risk assessment. Supplemental information has been included in the CIB (see *Section 4.2*) on the multiplication of uncertainty factors.

Stakeholders questioned the text in the CIB describing the use of UFs under several specific conditions or scenarios. These specific issues were: (1) UFs used to extrapolate for effect severity (i.e., what factor to use with a $BMDL_{10}$ or LC_{50} value); (2) UFs used to account for human variability (i.e., assumptions related to UFs to account for asthmatics, background exposures, etc.); and (3) UFs used to derive IDLH values for specific endpoints (i.e., irritants).

NIOSH Response: The majority of these comments were directed at text intended to provide only illustrative examples that were included in various sections of the CIB. The intent was not to provide strict rules for UF application, but rather to highlight key considerations applied during the derivation of IDLH values. In all cases, a weight of evidence approach is used on a case-by-case basis reflecting the nature (i.e., the strengths and weaknesses) of the available data. This weight of evidence approach serves as the fundamental basis of the IDLH derivation methodology outlined in the CIB, and differs from strict dictates regarding the application of a default UF for different scenarios. The description of this general approach has been strengthened in the CIB. For example, Appendix D has been expanded and modified. One modification, removal of a "preferred default" UF has been done to further highlight the data-set dependent nature of the UF application process. In addition, clarifications were added in the body of the CIB to better illustrate the application of weight of evidence as the fundamental principle for IDLH derivation.

Category 5: Chemical Mixtures and Other Stressors

Stakeholders inquired about alternative exposure situations or conditions that may cause IDLH values as derived to be inadequate to protect worker health. Examples of such scenarios identified by the stakeholders included (1) workplace exposures to multiple stressors that target the same organ system, (2) individual susceptibility associated with preexisting medical conditions or genetics, (3) biological rhythms, and (4) drug-chemical interactions. Their primary concerns focused on the desire for NIOSH to identify when such issues may cause the level of health protection offered by a specific IDLH value to be overwhelmed, with the result that workers might be at risk of serious health consequences at the IDLH concentration.

NIOSH Response: NIOSH recognizes the stakeholders' concerns regarding the identification of situations or conditions that may cause IDLH values to be inadequate for protecting workers' health from acute chemical exposures. A full evaluation of factors, such as alternative workplace exposures to hazards, biological rhythms, drug interactions, or genetic susceptibility, which may cause the protectiveness of a specific IDLH value to become inadequate, is not feasible with the current science. Many of the considerations raised are anticipated to be accounted for to some extent through the assignment of UFs (and in particular those relating to human variability in sensitivity). However, current IDLH values may not fully account for consideration of the combination of risk factors for a specific individual or scenario that increase health impacts of chemical toxicity.

Risk managers or other users apply IDLH values for countless workplace settings with varying conditions. For this reason, characterizing the uses of IDLH values and the wide level of variation that may occur within each setting is not possible and beyond both the scope of the IDLH CIB or the chemical-specific IDLH value support documents. As with other types of exposure guidelines, NIOSH recommends that all users of the IDLH CIB and the individual IDLH values invest sufficient time and resources to understand the scientific process used to establish the acute exposure limits. In doing so, the strengths and limitations of the IDLH values will be identified and better understood so that if other conditions arise that may invalidate their use or decrease the level of protection afforded users will be prepared to make alternative risk management decisions.

Stakeholders inquired about the inclusion of information regarding chemical mixtures that may result in IDLH conditions. More specifically, the stakeholders stated, *"Some exposure situations will include mixtures of chemical substances that might have combined effects (additive, synergistic, potentiating). Since the IDLHs are derived based upon exposure to one substance at a time, how should mixtures be handled? For instance, where the primary basis for the derivation of an IDLH in the documentation was the same as for another chemical within the mixture, should an additive effects formula be applied, e.g., that is if the sum of (C1/T1 + C2/T2 + ... Cn/Tn) exceeds unity, the IDLH limit of the mixture should be considered as being exceeded (where C1 indicates the observed atmospheric concentration and T1 is the corresponding IDLH)"*

NIOSH Response: NIOSH recognizes that exposures to chemical mixtures in the workplace may generate risks that are not addressed when evaluating the application of the IDLH value for a single chemical. Supplemental recommendations relating to chemical mixtures and IDLH values are not included at this time because of the absence of adequate data to develop a robust cumulative risk approach. Additional research on this subject may lead to further guidance on the adjustment or

combination of IDLH values to account for the increased risks of chemical mixtures. This has been recognized as an important data gap within the IDLH project and will be investigated more fully in the future.

Category 6: Relationship between the IDLH Values and Acute Exposure Guideline Levels (AEGLs)

A stakeholder raised concerns about the use of the AEGL standard operating procedure (SOP) and reliance on this resource as the basis of the IDLH methodology. More precisely, the stakeholder stated, *"My primary concern is the description and use of AEGL values as well as the application of AEGLs to a working population, individuals AEGLs were not intended for. AEGL values are derived for once in a lifetime or rare exposures to the general population. Although they are an excellent example of a starting point for the derivation of IDLH values, they must be examined on a case by case basis for use in any occupational setting. Specifically, in the occupational setting, there are a wide range of exposure scenarios that NIOSH needs to take into account, how IDLHs will be utilized in order to decide if AEGL values derived for a public single exposure are being properly used in a new occupational setting with multiple exposures."*

NIOSH Response: The AEGL SOP has been reviewed by the National Academy of Sciences (NAS) and is intended to represent the current best practices for setting health-based acute exposure limits for the general population and is based on the current state of science and knowledge. The AEGL SOP has been discussed in the context of the IDLH methodology, but it is not the exclusive basis of the IDLH methodology. Additional considerations to account for the intended purpose of an IDLH value (occupational setting vs. community/environmental setting), population of interest (workers vs. general population), time-adjustments, UFs, and data selection have been included in the IDLH methodology that vary substantially from the AEGL SOP. These points and the differences between the IDLH methodology and the AEGL SOP have been discussed in numerous locations within the CIB (see Section 2.1). Specific information provided outlining the differences between the AEGLs and the IDLH values include, *"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). IDLH values are designed for worker populations, which traditionally exclude the most sensitive subpopulations..."* and *"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."* These examples are provided in the CIB to demonstrate that despite the inclusion of a description of and some shared elements from the AEGL SOP (as well as other acute inhalation limits) in the IDLH methodology CIB there are distinct difference among the applications of these various exposure guideline resources.

NIOSH believes that sufficient information has been provided in the CIB to document the relationship between the AEGL SOP and IDLH methodology with a specific focus on the AEGL SOP serving as an important component of the IDLH methodology, but not as the sole line of evidence used to derive IDLH values. It should be noted that some reviewers endorsed the use of the AEGL methodologies in the SOP

for the derivation of IDLH values. Specific examples of such recommendations included reliance on separate default UFs and the application of the ten Berge approach for exposure-duration adjustment. The methodology discussed in the CIB takes into consideration both perspectives on the degree to which the AEGL SOP is directly adopted for the IDLH methods as deemed appropriate for purposes of their respective intended uses.

Category 7: Case Study (Appendix A)

Stakeholders provided numerous comments regarding the case study located in *Appendix* A of the IDLH CIB. Primarily, the stakeholders disagreed on the selection of vinyl acetate as the focus of the case study because of (1) the nature and shortcomings of available data and (2) technical issues, including assignment of UFs, selection of key studies, and duration-adjustments. Overall, the comments indicated that the stakeholders had sufficient disagreements with elements of this specific case study to indicate that an alternative illustrative example might be more appropriate.

NIOSH Response: The case study is intended to provide a practical example of the application of the IDLH methodology outlined in the CIB for derivation of an IDLH value for a specific chemical. After re-reviewing the case study and the data relating to vinyl acetate, NIOSH agrees with the stakeholders that vinyl acetate is not an appropriate subject for the case study for the reasons discussed above. Based on the stakeholders' comments, the vinyl acetate case study has been replaced with a case study for chlorine. The dataset for chlorine is significantly larger than vinyl acetate as chlorine has been evaluated in many diverse exposures. A common industrial chemical, chlorine, is a recognized acute toxicant that is often used as a relevant general example for risk assessment training and outreach for acute exposure scenarios. Moreover, the IDLH value presented in the case study aligns well with newer analysis of the acute hazards of chlorine conducted by other organizations, such as the AEGL committee.

Category 8: Data Quality and Selection

Stakeholders questioned the order in which NIOSH uses data for IDLH derivation as presented in the CIB. More precisely, in Section 3.4 – Determining the Critical Study and Endpoint, NIOSH provides guidance on the relative preference for selection of key study endpoints based on study quality and health endpoint relevance. A list provided in Subsection 3.4.2 provides a hierarchy intended to illustrate the data preferences for establishing an IDLH value. Stakeholders disagreed with the order of the data types and the wording NIOSH used to describe the hierarchy.

NIOSH Response: After reviewing the list included in Section 3.4.2, NIOSH agrees with the stakeholders' comments and has rearranged the order of the different types of studies. In the revised list, toxicity studies using oral dosing are the lowest level in the hierarchy. The new order is consistent with the stakeholders' comments.

Stakeholders recommended that NIOSH use only primary data sources to derive IDLH values. The stakeholders indicated that secondary sources, such as monographs or reports that summarize epidemiological and toxicological data, should be used only for background information or when primary data sources are unavailable.

NIOSH Response: NIOSH agrees with the stakeholders' comment regarding the use of primary data sources as the basis of IDLH values with secondary data sources being treated strictly as support for the value and rationale. The only exception reflects situations when primary data sources are unavailable and an IDLH value cannot be derived without being based on the secondary data sources. Additional information on this subject has been added to Section 3.4.2.

Stakeholders questioned the use of non-peer reviewed data and advocated that peer reviewed data be used as the primary basis of an IDLH value. More specifically, the stakeholders indicated that when both peer and non-peer reviewed data are available the peer reviewed data should be used as the basis of the IDLH even when the non-peer reviewed data may produce a feasible alternative IDLH value for the chemical. The argument being that the peer reviewed data has been subjected to a more rigorous review process and is in theory higher quality than non-peer reviewed data.

NIOSH Response: NIOSH agrees with the stakeholders' comment regarding the use of peer reviewed versus non-peer reviewed data sources as the basis of IDLH values. Peer-reviewed data sources are generally preferred. Peer reviewed studies take precedent over data that has not been peer reviewed, unless other issues are identified that give greater weight to the non-peer reviewed studies. For example, in section 3.4.1 of the CIB, NIOSH has included a list of key elements that are examined to determine a study's quality and relevance as the basis for an IDLH value including:

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

In the event that non-peer reviewed studies are determined to be of higher quality or relevance based on these key elements, then the IDLH value may be derived using the non-peer reviewed studies. The ultimate basis for the IDLH value will be determined based on the weight of evidence approach incorporated and described in the CIB. This data prioritization approach aligns with the nature of the stakeholders' recommendations regarding the derivation of IDLH values and ensures that the highest quality data are used to develop scientifically-defensible IDLH values. This general approach is also consistent with standard data quality evaluation tools and methods as cited in the CIB. Additional information on this subject has been added to Section 3.4.2.

Category 9: Point of Departure (POD) Selection and Weight of Evidence (WOE)

Stakeholders noted several specific issues that are embedded in the procedures for selecting the POD and application of the weight of evidence approach for specific endpoints and data types. One area of concern was the use of acute lethality data and identifying the human threshold for this effect. The stakeholders questioned the POD metrics noted in the CIB for lethality, extrapolation methods from these various metrics, and the use of LC_{lo} values within the derivation of the IDLH values. The stakeholders identified a

peer reviewed study (Rusch et al. 2009) that investigates questions of estimating lethality thresholds from LC50 values and suggested its inclusion within the CIB as guidance.

NIOSH Response: The stakeholders' comments address the need to develop or identify the best estimate of the human lethality threshold. Basically, the metrics for each individual study vary although the CIB does provide guidance on selecting a preferred endpoint as the POD (see Section 3.4.2). Potential endpoints and metrics are not equivalent and vary with the nature of the data set. For this reason, the goal is to identify the highest concentration that will not cause lethality. Nevertheless, regardless of the nature of the data set a weight of evidence approach is applied to identify the best POD as well as the appropriate UF to apply to estimate a sub-lethal concentration in humans. In addition, the article identified by the stakeholders (Rusch et al. 2009) has been reviewed and included within the CIB (see Section 3.4.2.1.2).

Individual stakeholders questioned specific examples included in the CIB to illustrate the assignment of potential of UFs during the derivation of IDLH values as applied to certain POD estimates.

NIOSH Response: The examples are intended to illustrate key considerations, approaches, or concepts applied within the derivation of IDLH values. The rationale included to describe the key consideration that is the focus of the example is truncated when compared to the discussions that are included within the individual support documentation for a specific IDLH value (See Appendix A – Case Study). Inclusion of the full details associated with a specific example would result in a lengthy discussion of the quality of data, findings of the weight of evidence approach, discussion on the limitation of the data along with other additional commentary on the data set that would distract from the key consideration that is the intended focal point of the example. Although the stakeholders' questions were noted, inclusion of the supplemental data is not needed within the CIB to illustrate the key consideration discussed. To communicate this more clearly the intent of the examples is highlighted in the CIB. A specific IDLH value has been included in all support documentation as illustrated by the case study found in Appendix A of the CIB.

One stakeholder discussed the difficulty in using developmental toxicity data as the basis of acute exposure guidelines, such as IDLH values. As indicated by the stakeholder, use of such data often includes a large level of uncertainty. The stakeholder recommended several studies be reviewed and incorporated into the CIB to provide supplemental guidance. These studies included Davis et al. (2009) and Van Raaij et al. (2003).

NIOSH Response: The recommended references have been reviewed and cited in the CIB (see Section 3.4.2.1.4) as additional resources that help inform the weight of evidence approach for developmental toxicity endpoints. Based on the information contained in these studies, other specific methodology changes were not deemed necessary. No additional changes regarding developmental toxicology considerations have been made within the CIB.

Category 10: Duration Adjustment (Time Scaling)

Overall, the stakeholders agreed with the approach discussed in the CIB (Section 3.5) and the use of the ten Berge equations to scale available data to a 30-minute concentration that serves as the basis of an IDLH value. The ten Berge equations modify Haber's rule (concentration * time) to include an exponent

("n") that modifies this relationship. As discussed within the CIB, default "n" values are applied when empirically-derived values are unavailable. The derived "n" values are often based on modeling of lethality data associated with a specific test species. Stakeholders questioned the procedures in the CIB for use of derived "n" values for duration extrapolation of non-lethal effects and across studies of different animal species.

NIOSH response: One of the key issues that must be taken into consideration for the selection of default versus empirically-derived "n" values focuses on the mode of action for the various toxicological endpoints concerned. If the mode of action for the critical non-lethal effect is determined to be the same mode of action that caused lethality then the CIB allows for the use of an empirically-derived "n" value from the lethality data. In the event that the mode of action varies between non-lethal effects and lethality or is unknown, the CIB recommends the use of the default "n" values. Along with other key judgments, the ultimate selection of the duration extrapolation approach is made on a case-by-case basis using the data available for the specific chemical.

Stakeholders stated that due to the mechanism of action for irritants additional considerations are need when applying duration adjustment for this endpoint (see *Section 3.5 – Time Scaling*). More specifically, flattening the time-extrapolation curve for irritants is relevant for mild irritant effects (sensory irritants). This is not the case for severe irritant effects that are on the edge of irreversible and possibly escape impairing effects. The stakeholder indicated that concentrations that cause moderate or severe irritation should be time scaled because the effects are dependent on both the concentration and duration of exposure.

NIOSH response: NIOSH agrees with the stakeholder's comment regarding duration adjustments of irritants. In short, time scaling using the ten Berge equations is applied when the effects are categorized as severe irritation and may cause irreversible injury to exposed tissue. Additional information has been included in the CIB on this subject matter to provide further guidance on the development of IDLH values based on irritation.