Attachment D: NIOSH Response to External Peer Reviewers' 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 health-based IDLH values. The finalized CIB supersedes previous NIOSH policy on the derivation of IDLH values. The NIOSH policy and resulting IDLH methodology was last updated in 1994 [NIOSH 1994][1].

The intended audience for the draft 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 draft 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 External Peer 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 stakeholders were received by the NIOSH Docket Office for the IDLH CIB, NIOSH Docket #156. No comments were received from the public.

In total seven subject matter experts in the fields of toxicology/pharmacology, risk assessment, industrial hygiene, and statistics were approached with the request to serve as peer reviewers of the draft CIB. Two of the subject matter experts consented to participating in review. These peer reviewers received 1) the draft CIB and 2) a summary of the stakeholders' comments. NIOSH requested that peer reviewers provide comments on both the draft CIB and supplemental information that summarized key consideration identified in stakeholder's comments. Overall, the peer reviewers' comments were strongly supportive of the draft CIB and the protocol developed by NIOSH for the derivation of IDLH Values. Section 3.0 provides the verbatim comments from the peer reviewers coupled with the NIOSH responses.

3.0 Category Summary and NIOSH Response

This section contains the verbatim comments received from the two subject matter experts that participated in the peer review of the draft CIB. Table 3.1 contains the comments from reviewer #1, while Table 3.2 contains the comments from reviewer #2. NIOSH's response to the reviewers' comments are located within the third column (blue text), while the specific sections of the draft CIB where the comment/responses are identified are in the last column (**bold text in blue**).

[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.*

Table 3.1 – Verbatim Comments from Reviewer #1 with NIOSH Response

Comment #	Comment	NIOSH Responses	Location within Draft CIB
1-1	**In response to a question from NIOSH inquiring if additional information or guidance is needed within the draft CIB, the reviewer stated,** "Overall, this is a very well written document that clearly outlines the methodology involved in the derivation of IDLH values. A number of clarifications related to choice of key study need to be made, as indicated in specific comments below."	We thank the reviewer for indicating that the draft CIB is a well written document. In addition, the clarifications alluded to by the reviewer regarding key study selection are addressed in subsequent comments.	**N/A**
1-2	**In response to a question from NIOSH inquiring if the data cited within the draft CIB support the objectives of the document the reviewer stated,** "The data cited do support the objectives of the document."	No response required.	**N/A**
1-3	**In response to a question from NIOSH inquiring if the protocol outlined in the draft CIB support the development of health protective IDLH values in light of the current understanding of the toxicological data and application of the principles of risk assessment the reviewer stated,** "This may be better addressed pending the response to a number of issues noted below."	No response required. Addressed in subsequent comments.	**N/A**
1-4	**The following comments are identified by the**	N/A	**N/A**

	reviewer as issues that need clarifications.		
1-5	"Table 2.1 – The Table is noted to present Short Term Limits but includes TLVs, which are long term exposure guidelines."	The first column within this table is titled, "Purpose of Short-term Exposure Limit," and provides a description of a group of short-term exposure limits included within Table 2.1 as stated for the group that includes the threshold limit values (TLVs), "Acute exposure guidelines for potential routine acute exposures in the workplace such as short term exposure limits (STEL) or Ceiling Limits ("C")." STELs are occupational exposure limits, including certain TLVs, designed to provide recommendations for acute exposures to airborne contaminants. The description of this table is not incorrect, but we understand the reviewer's confusion. Many people think of TLVs referring only to the 8-hour time weighted average (TWA) occupational exposure limits that are intended for repeat exposure scenarios (non-acute). No change made to this table.	**Chapter 2.0**
1-6	"The AEGL is a Committee not a subcommittee as stated in the document."	The reviewer's comment was correct and the error has been corrected.	**Section 2.1**
1-7	**In reference to the following statement included within the draft CIB – *"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"*, the reviewer stated,** "This sentence is not clear".	This statement has been rewritten to clarify the intended message. The replacement statement is as follows, "The use of a weight of evidence approach allows for the integration of all available data that may originate from different lines of evidence into the analysis and the subsequent derivation of an IDLH value. Ideally, this ensures that the analysis is not restricted to a limited dataset or a single study for a specific chemical."	**Executive Summary & Chapter 3.0**
1-8	"The distinction between mode of action (MOA) and mechanism of action gets a bit muddled in this section. For example, a MOA would be effect on the nervous system, while a mechanism of action for this would be CNS depression."	The reviewer's comment is noted and appreciated. After reviewing this section, it was determined that sufficient information has been included to differentiate between the terms "mode of action" (MOA) and "mechanism of action".	**Section 3.1**

		We agree with the reviewer that "mode of action" refers to a less specific level of knowledge than "mechanism of action". The draft CIB specifically states, "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 current CIB uses the term MOA and implements the concepts for MOA in a manner consistent with the IPCS (2007) Mode of Action and Human Relevance Framework. In regards to reviewer's comment about the nervous system effects as an example of a MOA, we also note that in current risk assessments that apply MOA assessment frameworks (e.g., developed by the IPCS) the overall level of biology knowledge used to define a MOA has increased beyond the example given by the reviewer. A statement such as "effects on the central nervous system" would in the context of current risk assessments be considered a description of the target organ or system. Even the phrase "central nervous system (CNS) depression" is not fully adequate as a description of a MOA – since the important element of defining a "series of measurable key events" is not included. However, since CNS depression is linked to measurable key events it is a reasonable descriptor as a MOA for the purposes of the analysis in the CIB, since it describes a specific (distinguishable) effect on the CNS.	
1-9	"Low level exposures to some chemicals may result in toxicity to other organs. Thus, it is not only high level exposures, which is undefined, here, that may be of concern. Furthermore, this entire section should be combined with the next one into a Systemic Target Organ effects	After reviewing the section identified by the reviewer, it was determined that modifications were needed to better explain the role of mode of action considerations relating to target organ toxicants. As suggested by the reviewer, the Systemic Target Organ Effects Section has been combined with the	**Section 3.1**

	section."	Target Organ Toxicants Section. This has allowed for a more complete description of the effects covered by these sections and addressed them as a continuum of effects.	
1-10	"Sensory irritation does not show small variability in the human population. There is quite a large variability for this endpoint."	This statement – originally included as an example of mode of action (MOA) considerations – has been removed from the draft CIB. In addition, supplemental language on sensory irritants has been included within this section.	**Section 3.1**
1-11	"What is meant by '...human and toxicity information...?"" This statement refers to the first sentence in Section 3.3 that describes the purpose of the literature search.	This statement has been modified to clarify its meaning.	**Section 3.3**
1-12	"There may be some confusion in the document when it notes here that there is selection of a 'critical study" to serve as the basis for the IDLH when later it is noted that derivation of the IDLH involves a 'weight of evidence' approach. This latter does not necessarily depend upon a single critical study."	The weight of evidence approach is applied during the derivation of the IDLH values to identify the strengths and weaknesses associated with each line of data (study). In addition, it provides guidance for selection and application of uncertainty factors (UF) along with identifying key considerations that need to be addressed. By applying the weight of evidence approach, we are guided to the "critical study" that serves as the basis of the IDLH value. In the case of the IDLH values, a single critical study was selected using the weight of evidence approach. As defined within the Glossary, the "critical study" is defined as the "study that contributes most significantly to the qualitative and quantitative assessment of risk." Additional information has been included within the draft CIB to describe the relationship between the use of a weight of evidence approach and the critical study.	**Section 3.4** **(Stakeholder Topic 4 – Uncertainty Factor)**

1-13	"The use of oral toxicity data to derive inhalation guidelines is rarely appropriate and can only be used under specific circumstances. Thus, the position in the hierarchy is too high."	NIOSH agrees with this comment and we have corrected the order of the data hierarchical approach discussed within the draft CIB so that oral data are listed as the lowest form of data preferred to derive an IDLH value. This comment aligns with concerns raised by stakeholders.	**Section 3.4.2** **(Stakeholder Topic 8 – Data Quality and Selection)**
1-14	"It would be best to indicate a specific value between 10 and 20 rather than providing the comment that the value would be somewhere between 10 and 20."	NIOSH agrees with this comment and we have corrected this statement to indicate that the "appropriate IDLH value would be ~20 ppm." This change aligns with the reviewer's comment. It should be noted that this also aligns with concerns raised by stakeholders.	**Section 3.4.2.1**
1-15	"This paragraph should be moved to section 3.4.2.2." This statement refers to the following paragraph that has been included within Section 3.4.2.1.4 "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."	After reviewing Sections 3.4.2.1.4 and 3.4.2.2, we have concluded that the reviewer's suggestion to move the identified paragraph to section 3.4.2.2 would be ideal. In doing so, the discussion regarding repeated-exposure studies is strengthened.	**Section 3.4.2.2**

1-16	"This paragraph contradicts itself. First it notes that a 30 min inhalation study may not be available, but then it goes on to note that preference would be given to studies involving the duration of interest, which is 30 min."	This statement refers to the second paragraph located within Section 3.4.2.2. The intent of this paragraph is to discuss considerations relating to exposure duration and study quality. More precisely, this paragraph illustrates that preference is given during the derivation of an IDLH value to high quality studies that align with the duration of interest (30 minutes) or involves the minimal duration extrapolation. For example, if two studies are identified that have exposure durations of 20 minutes and 4 hours, preference will be given to the 20 minute study since it more closely aligns to the duration of interest (20 minute). The reviewer indicates that this paragraph contradicts itself. After reviewing the paragraph in details, it was decided that minor changes in the wording were needed to better convey the intended message.	**Section 3.4.2.2**
1-17	"This sentence does not make sense. If one cannot perform route to route extrapolation for irritants, then why can one perform such extrapolation in repeated studies for sensory irritants?"	Additional language has been included to address the reviewer's concerns regarding route-to-route extrapolation for irritants. In short, this issue is addressed via the inclusion of the following statements: 1. *For route-to-route extrapolation: It is inappropriate to conduct route-to-route extrapolation for irritants because they target the portal of entry.* 2. *For duration extrapolation: It may be appropriate to extrapolate from repeated-exposure studies for irritants, since concentration is often a more important determinant of irritation than exposure duration. Irritation effects observed on the first day*	**Section 3.4.2.2** **(Stakeholder Topic 2 – Route to Route Extrapolation)**

		of exposure during a repeated-exposure study may be used as the basis of an IDLH value.	
1-18	p.51, l.17-24. The circumstances under which route to route extrapolation may be used need to be better defined. For example, it is not noted that such extrapolation is not appropriate if there is a first pass effect from ingestion that would not occur in the lungs.	Additional language has been included within the route-to-route extrapolation section of the draft CIB. This additional language is intended to provide supplemental details on when it is appropriate to conduct route-to-route extrapolation and considerations associated with data selection.	**Sections 3.4.2.2, 3.4.2.4; Appendix E.1** **(Stakeholder Topic 2 – Route to Route Extrapolation)**
1-19	p.59. The three specific examples should be moved to an Appendix section.	These examples are intended to illustrate the impact of the "n" value on duration adjustments. Appendix A is intended to illustrate the entire process of deriving an IDLH value for a selected chemical. Including these examples within Appendix A would distract from its purpose. These examples have been moved to Appendix E, which has been included to provide supplemental information on specific topics and considerations applied during the derivation of IDLH values.	**Section E.2** **(Stakeholder Topic 10 – Duration Adjustment)**
1-20	"Table C-1. There are a number of inconsistencies in this Table."	These numbering inconsistencies have been corrected during the editing of the draft CIB.	**Table C-1**
1-21	"Lassitude may also be escape impairing."	Within the draft CIB, lassitude is used to describe the feeling of low energy, mild fatigue or lethargy. Extreme drowsiness, fatigue, or sleepiness is considered to be severe lassitude and is described as somnolence. This distinction has been made	**Table C.1**

1-31	Clearly, IDLH values must be based primarily upon health effects data. However, it would not be appropriate to ignore safety issues such as LEL when deriving IDLH values if the IDLH was above some fraction of the LEL. However, what that fraction should be may be the subject of discussion. The document must be clear in indicating when a safety issue must be considered in deriving the IDLH.	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	**Section 1.3** **(Stakeholder Topic 3 – Safety Issues [LEL])**

		publications. For dusts the application of a default approach based on 10% of the LEL is not appropriate. 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/).	
1-32	The AEGL process for AEGL 1, which considers irritation that does not impair the ability to	This comment addresses two issues. The first issue revolves around the continuum of effects associated with irritants; the	**Sections 3.1, 3.5**

	escape, does not consider duration in irritant response, and that is an appropriate approach for the IDLH as well.	second issue addresses time scaling (duration adjustments) for irritants. First, the severity of effects described by the reviewer (irritation that does not impair the ability to escape) does not meet the requirements to serve as the basis of an IDLH value. Instead, such information would be considered and incorporated into the weight of evidence approach applied to derive an IDLH value. Additional information has been included within the draft CIB to address concerns raised by stakeholders. This additional information provides supplemental insight into the continuum of effects associated with irritants and considerations when establishing IDLH values. Second, regarding duration adjustments for irritants, it has been demonstrated that irritation may be influenced more by the exposure concentration than exposure duration. When such conditions are identified, duration adjustments may be unneeded. This approach aligns with the Acute Exposure Guideline Levels (AEGL) Standing Operating Procedures (SOP).	**(Stakeholder Topic 6- Relationship between the IDLH values and AEGL values)**
1-33	My opinion is that the best approach is the one used in developing AEGL values, which is Method 3 in Attachment B. This basically assumes default values for UFs and then revises them based upon each chemical data set. This provides the best scientific justification of the proposed approaches.	This comment is in response to a question from NIOSH on which approach should be used for the selection of uncertainty factors (UFs). NIOSH has selected a hybrid approach that provides a data-informed starting point for the analysis, supported by empirical analysis. 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	**Appendix D.2** **(Stakeholder Topic 4 – Uncertainty Factors)**

		transparency over the weight of evidence approach, without requiring significant effort to explain departures from rigorous defaults that are 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 bases are 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.	
1-34	Given the temporal and spatial variability in potential background exposures, any process that attempts to take these into consideration in the derivation process for IDLH value may introduce more error than a procedure that does not take background into consideration. Thus, the best approach would be to incorporate potential background exposures into the UF for variability of response.	NIOSH is in agreement with the reviewer's comment and believes that the use of uncertainty factors (UFs) outlined within the draft CIB should provide a sufficient level of health protectiveness to account for background exposures and cumulative risk from other stressors. It should be noted that similar comments were received from a stakeholder reviewer.	**(Stakeholder Topic 4 – Uncertainty Factors)** **(Stakeholder Topic 5: Chemical Mixtures and Other Stressors)**
1-35	The proposed logic that smaller UF values for irritants may be justified since at lower doses the effects seen are at the portal of entry where there may be small differences in dosimetry between individuals is flawed. It is clear from the toxicological literature that there can be very wide differences in response for direct acting irritants that produce no systemic response. Thus, the UF for such irritants cannot be set at a lower value than that for systemic toxicants. The most conservative approach in the case where chemical specific data are not available is to use a chemical class approach, such that for all direct acting	NIOSH agrees with the reviewer that significant variability in human response to irritants can exist. Although in general the toxicokinetics portion of the variability for direct acting toxicants may be less than for systemic toxicants based on basic biological principles, as pointed out by the reviewer this will not be true for all chemicals. In most cases we will not have data to estimate the degree of variability in human response. As a result, the language identified by the reviewer has been removed. The methodology highlighted in the CIB focuses on selection of UF for each assessment through a weight of evidence approach taking into account chemical	**(Stakeholder Topic 4 – Uncertainty Factors)**

	irritants unless data indicate otherwise, an interindividual UF of 10 should be used.	specific information with preferred ranges as noted in the CIB. Thus, as recommended by the reviewer, the current methodology does not have a different default UF for irritants versus systemic toxicants.	
1-36	As with AEGL values, the default should always be 10	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	**(Stakeholder Topic 4 – Uncertainty Factors)**

		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 bases are 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.	

Table 3.2 – Verbatim Comments from Reviewer #2 with NIOSH Responses that Address Key Considerations Identified within Stakeholders' Comments

Comment#	Comment	NIOSH Responses	Location within Draft CIB
2-1	p. xxix (row 23): Uncertainty factors may be more clearly distinguished from or defined in relation to other types of assessment factors such as molar adjustment factors, modifying factors and safety factors.	The reviewer's comment was considered, but no change was made. It was decided that the current definition was sufficient. The use of supplementary terms, such as *modifying factors* and *safety factors*, could be confusing. In addition, these terms are not commonly applied in the modern practice of risk assessment and are terms that have been replaced by the term *uncertainty factors*. For example, the Acute Exposure Guideline Levels (AEGL) Standing Operating Procedures (SOP) does not use these terms.	**Glossary** **(Stakeholder Topic 4 – Uncertainty Factors)**
2-2	p. 15 (row 4 and onwards) The document mentions one of the major differences between the AEGL and IDLH programs; the target group. While AEGL is designed to protect the general population, incl. potentially susceptible subpopulations, the IDLH is designed for worker populations, which is assumed to be less sensitive on average than the general population. Although we agree that the working population is generally less susceptible, we suggest that this difference is more clearly evaluated since some susceptible groups may well be included in the working population. For example, parts of the elderly population may still be part of the working population; in addition some working individuals may have existing health impairments such as heart disease or asthma.	The reviewer's comment and concerns regarding the inclusion of susceptible sub-populations, such as the elderly, within the working population is noted. It is believed that the inclusion of uncertainty factors (UFs) during the derivation of IDLH values should account for this susceptible sub-population. More specifically, UFs that account for human variation and susceptibility are included within the derivation process.	**Section 2.1** **(Stakeholder Topic 4 – Uncertainty Factors)**

2-3	p. 16 (row 1 onwards) The document describes the AEGL process as before November 2011. Currently, we have received information that the NAC/AEGL committee will no longer be operating. This may unfortunately over time erode the quality and acceptance of AEGL values. Nevertheless, the SOP of AEGL is still a very useful reference document.	The reviewer is correct that mission and scope of the AEGL committee has changed and they will have limited activities in the future. Despite this fact, the process outlined in the Acute Exposure Guideline Levels (AEGL) Standing Operating Procedures (SOPs) represents one of the most current protocols for establishing acute exposure guidelines. Its continued inclusion within this draft CIB is to be expected for this reason and it serves as one of many sources of information used to derive IDLH values.	**Section 2.1** **(Stakeholder Topic 6- Relationship between the IDLH values and AEGL values)**
2-4	p. 14-18 Please consider to refer to a paper with a comparative analysis of the difference between AEGL and ERPG. (Öberg et al., 2010, Discrepancy among acute guideline levels for emergency response, J. Haz. Mat. 184:439-447)	As requested by the reviewer, this study has been included within the discussion on Emergency Response Planning Guidelines (ERPGs) and the Acute Exposure Guideline Level (AEGL) values.	**Section 2.1** **(Stakeholder Topic 6- Relationship between the IDLH values and AEGL values)**
2-5	p. 20 (row 22) It is stated that table 2.4.1 include values for general population. Is SMAC values developed for general population?	The description of the acute inhalation exposure limits/values has been modified to ensure that their intended uses are reflected accurately within the draft CIB.	**Section 2.4; Table 2.4.1**
2-6	p. 29 (ch. 3.3.) According to our experience, it is very valuable to include a search of the reference lists in other relevant criteria/risk assessment support documents, since the databases listed (Tab. 3.3.1. are not covering all the toxicological testing literature).	Table 3.3 is intended to illustrate key resources used to identify data on the chemicals of interest being evaluated for IDLH value. This list is not intended to be exclusive or static. As new resources are identified, they will be incorporated into the literature search sources for future evaluations.	**Section 3.3.1**

		Additional language to reflect the dynamic nature of this list has been included to provide supplemental information on the literature search within the draft CIB.	
2-7	p. 68 (row 3) If the POD is from a sensitive group is used, is it possible that the UF could be lower than one?	An uncertainty factor (UF) less than 1 would not be ideal since it would actually raise the IDLH value and would be less health protective. The value of 1 to account for sensitive/susceptible sub-population is the lowest UF that will be applied in the derivation of an IDLH value.	**Chapter 4.0** **(Stakeholder Topic 4 – Uncertainty Factors)**
2-8	p. 70 (row 3 onwards) In our paper (Öberg et al., 2010) we try to describe the implicit UFs in the ERPG process. To avoid the similar lack of transparency as seen in the ERPG documents, we suggest that a standard support document for derivation of IDLH should at least shortly comment of all appointed areas of variability (inter- and intraspecies variation etc.)	For each IDLH value developed based on the protocol outlined in the draft CIB, a support document will be developed that identifies key studies, explains the use of uncertainty factors, highlights critical considerations/assumptions, and other relevant information. For an example, please see Appendix A.	**Appendix A** **(Stakeholder Topic 7 – Case Study)**