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From: Ernest V. Falke [basinfalke@comcast.net]
Sent: Tuesday, March 01, 2011 9:47 PM
To: NIOSH Docket Office (CDC)
Subject: 156 - Current Intelligence Bulletin (CIB): Derivation of Immediately Dangerous to Life and Health (IDLH) Values - Comments
Attachments: IDLH CIB review Jan-2011 falke.pdf

Dear Sirs:

Attached are my comments.

Ernest V. Falke

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Review of:

Current Intelligence Bulletin (CIB): Derivation of Immediately Dangerous to Life and Health (IDLH) Values. Draft dated 12/06/11

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-NOTE – Comments below reflect the opinion of Ernest Falke and not of the US Environmental Protection Agency. They have not been reviewed by EPA management.

-Rather than write page in front of the number, I have used shorthand where the first number to the comment refers to the page and the second number to the line(s).

-General Comment: The document does a good overall job of pulling together the methodology used to derive IDLHs and provides transparency. The major concept that should be further amplified in this or a future document is the rationale for total Uncertainty Factor selection.

1) vi 23-27. Please change the following phrase *"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)."* to *"Incorporated with the updated protocol are the standing guidelines and procedures (NAS, 2001) used for the development of community-based acute exposure limits called Acute Exposure Guideline Levels (AEGLs)."* The AEGL values are developed by the NAC Committee for Acute Exposure Guideline Levels. This is a FACA committee output that is then reviewed and published by the NAS. EPA administers the program in trust to meet the needs of a number of federal agencies. These are not EPA numbers but represent something unique in the federal government; federal agencies with a common need working together to provide a unified output to meet that requirement.

2) xvii 5-9. Please rephrase *"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)."* to "*Acute Exposure Guideline Level (AEGL): Tiered guideline levels for exposures to airborne substances intended to provide estimates of threshold concentrations and exposure durations (10 minutes to 8 hours) for discomfort, disability, and death in the general population."* The definition you use is probably from the SOP but it is wordy and lacks definition. The second phrase more accurately reflects what AEGLs are intended to represent.
3) xvii 19. The low end of your acute toxicity definition is for 24 hours for exposure yet the IDLH is for 30 minutes. Exposure duration might better be stated as minutes to hours of exposure.
4) xvii 25. Shouldn't the definition of IDLH value include duration? It is for 30 minutes exposure. This is important because an acceptable level for 30 minutes of exposure might be unacceptable for exposures lasting 1 hour or longer.
5) 10 24-28. It looks like the toxicity based value and statement about exceeding the 10% LEL would be included but it is unclear whether the actual 10% LEL would be stated. That value should also be in any documentation or table.
6) 26 16-19. You seem to differentiate between "sensory irritants" and "reactive gasses". Most irritating chemicals cause a spectrum of effects with increasing severity at increasing doses. You cite choloropicrin as an irritant but at higher doses it causes death through severe lung damage, presumably reacting with the lung tissue. Even "reactive gasses" will trigger the trigeminal nerve at low doses without causing tissue damage.
7) 28 6-7. The smaller UF for irritants may be justified because at lower doses the effects seen are at the portal of entry where there would be small differences in dosimetry between individuals and the fact that metabolism is usually not a factor because the chemical acts directly on the tissue. This needs to be considered carefully and is not always true. For example, asthmatics are over 10 times more susceptible to sulfur dioxide exposure than non-asthmatics.
8) 28 8-11. Flattening the time-extrapolation curve for irritants is relevant for mild irritant effects. However, for more severe effects that are on the threshold of irreversible effects and perhaps impairment of escape (IDLH levels), there is probably a relationship where n varies between 1 and 3 ($C^n \times t = k$). The IDLH is analogous to the 30 minute AEGL-2. The AEGL-2 is typically scaled for irritants, not flat-lined, because you are at the threshold for serious irreversible effects. Induction of these effects usually shows both a concentration and time component.
9) 28 12-14. Although not stated, you are implying that route-to-route extrapolation might be appropriate in some situations. Generally this approach is ill advised unless there are no inhalation data and a compelling need to develop an IDLH. Going from oral to inhalation values may be better than nothing but holds massive uncertainties.
10) 28 15-18. Other examples include the release of HCl from chlorosilanes or the release of phosphine from metal phosphides.

11) Table 3.3.1. Also include EPA TSCA 8(e) notices that are available online. See also section 3.2 of the AEGL SOP for ideas. Another major source is from unpublished industry studies. NIOSH should be in a good position to interact with industry and access any information they might have.
12) 33 13-20. I agree that you may not select the study giving the lowest IDLH value because of study quality considerations. It is important to emphasize that alternative approaches were considered and why you made the selection you did.
13) 34 3. I would put acute animal oral toxicity at the bottom of the list. For AEGLs we have used oral data only for methanol where there was a well documented poisoning incident with blood level monitoring and pharmacokinetic modeling to predict inhalation exposures that would have given the toxic blood levels. It is however the least reliable of the methods you list. That being said, you will sometimes have the requirement of developing some level and must use the oral data. In such cases, there should be a caveat to the value and industry encouraged to develop the relevant data. I doubt you have the legislative authority to do so but voluntary negotiations can sometimes work wonders. Dr. Pauluhn in Germany has published on this issue. While he argues against using oral data, you will sometimes have no choice. He might be able to suggest means to temper the extrapolation.
14) 35 4-15. Your discussion is well put but you back off from drawing a conclusion. Something you must do when you set an IDLH. Given the data set you described the best POD would probably be 20 ppm. I agree that an UF of 3 might be too high given no irritation at 10 ppm. However, you have to consider the population under study. Did it include a known susceptible group such as asthmatics? Asthmatic susceptibility to irritants can vary between 1 to 10-fold (probably higher in the case of SO2) higher than non-asthmatics. If the study was done on a non-asthmatic population, you should use a UF of at least 3-10 in the absence of other information. A bad asthmatic attack can severely inhibit the ability to escape.
15) 36 19-26. Cite the AEGL SOP. It gives a justification for the approach you are taking. A further caution when using this methodology. Always compare the benchmark dose extrapolation with the experimental data. We sometimes find the statistical modeling at such variance with the experimental data it is deemed unreliable.
16) Section 3.3.2.1. Consideration of lethality data.
    a) The AEGL-2 for 30 minutes is analogous to the IDLH. We take 1/3 of the estimated lethality threshold as an estimate of the threshold for irreversible effects. See the AEGL SOP for documentation on this.
    b) Use of LC50 data when no other data exist. You mention using a higher UF when this is done. Rather you should divide the LC50 by 3 to obtain an estimate of the lethality threshold. This is a good rule of thumb. Dr. George Rusch at Honeywell recently published an article documenting this relationship. You should divide the LC50 to obtain the estimated lethality threshold and reference his publication for support.
17) 39 8-20. This is a good discussion of the RD50 and a pragmatic approach to its use.
18) Section 3.4.2.1.4. The discussion of developmental toxicity is well taken. This is a difficult area and usually what you do it fraught with a lot of uncertainty. In table 3.4.3.1.4 add a column with the UFs used to derive the IDLH values. In your data set

the derivation from the developmental toxicity study is close to that derived from the LC50 data. It will not always be that easy. You may want to consult the following for consideration and guidance:

a) Van Raaij in RIVM report 601900004/2003. The relevance of developmental toxicity endpoints for acute limit setting.
b) Davis in Regulatory Toxicology and Pharmacology 54 (2009) 134–142. The role of developmental toxicity studies in acute exposure assessments: Analysis of single-day vs. multiple-day exposure regimens

19) 44 4-12. Excellent discussion of how data can be integrated into a weight of evidence approach.
20) 46 5-7. Irritation at low levels that are irritating is generally concentration, not time, dependent. IDLH type effects will probably occur at higher doses where compensatory detoxification mechanisms are overwhelmed. In that case time dependence may enter. However, if you use multiple exposure studies to set an IDLH value assuming concentration dependence, your values will be at least conservative since most multiple exposures will be in the 4-6 hour range and you are extrapolating to 30 minute exposures. As you indicate earlier, careful consideration of the mode of action and data set on a particular chemical is paramount.
21) Table 3.4.2.2. The discussion around this table on the previous page is excellent. In the table add a column with the UFs used so the reader can see how get from point A to point B. In a complete document you would have to not only describe the UFs used by why they were reasonable.
22) Section 3.4.2.4. This is an excellent discussion of a difficult issue. See also comment on 34 3. above. Extrapolating from oral to inhalation should have a more rigorous evaluation. As indicated above I think Pauluhn has published on this as well as others. It would be helpful if federal offices that need to do this type of extrapolation could get together and jointly develop an analysis of this topic to identify strengths, weaknesses and better default approaches from such an analysis. Such extrapolations are not the best science but better than nothing when data are lacking. Programs that immediately come to mind are IDLH (NIOSH), the new chemicals program under TSCA (EPA), maybe pesticides (EPA), and other entities. Such an analysis would be a cost effective use of taxpayer dollars to address an issue of importance to a number of agencies in the government. The analysis could be peer reviewed and a joint procedure established that is uniform throughout the government. Other countries might also be willing to contribute to this effort. What a radical thought that the federal government could work together jointly.
23) Section 3.5 Time Scaling – You might note that n is usually derived from LC50 data with death as an endpoint. IDLH values are based on effects of lesser severity. However, since the IDLH endpoint is on a continuum through death and is perhaps within a factor of 3 of the endpoint of death, the value of n for the IDLH endpoint is assumed be the same as the one for death. The AEGL SOP discusses this better but you should make the point.
24) 66 14-16. You note a 3 is really 3.16 but you should amplify that is why 3x3=10. Otherwise the reader won't understand why 3x3x3=30 instead of 27.
25) Table 4.2.1 Typical Uncertainty Factor Ranges – This should be broken down into the separate factors so the reader knows how you derived the value stated and can adjust

up or down according to the data set. Rather than discuss each scenario, there seems to be a consistent use of an UF of 1 for human variability. Even for a worker population this seems a bit low as a default for the preferred UF. A 3 might be more appropriate.

a) For example, you use 30 for the LC50. I assume the 30 comes from a 3 for estimating the non-lethal level (George Rusch published a paper that documents this - Regul Toxicol Pharmacol. 2009 Aug;54(3):247-55. Epub 2009 May 8.), a further factor of 3 for estimating the threshold for irreversible effects (discussed in the AEGL SOP) and a 3 from extrapolating from animal to human. However, this leaves out the additional 3 for human variability. Is that what you intend? The UF in this case would be 100 from an LC50 rather than 30. This approach would be consistent with what might be done with AEGLs. If you have reason to justify the 30 then it should be developed – see comments below.
b) LC01, LCLo, BMCL10 for lethality in animals. There are a number of factors to consider here. At the least the preferred factor seems to leave out human variability if all of the UFs are assigned a 3. I assume the endpoints are designed to define the highest dose that does not cause lethality in animals. Your intent is to go on from there to define an irreversible effect threshold and then apply animal to human and human variability UFs. Regardless, you should specify the UF you apply to each level of uncertainty and the rationale for selecting that UF. You can later change the total UF based upon a weight of evidence analysis.
    i) First – all of the endpoints are not equivalent. Your goal is to identify the highest exposure that will not cause lethality. In the AEGL program that can be either the BMC01 or BMCL05 when BMC modeling is done. In that case we choose the lowest of the values. This is covered in the AEGL SOP (search for Fowles – he did the study to support this conclusion).
    ii) The BMCL10 you cite is too high to estimate the non-lethal level. Granted the default in BMC modeling is the 10% response. However, this must be tempered by the effect under consideration. For example, a statistical evaluation of the lethality literature indicates that when computing the BMCL, the value for the response should be 5%, not 10%. If you were modeling the Functional Observational Battery, the value would be the 20% response because of the high background and variability in the FOB assay. The level of response will change according to the background for the effect under consideration.
    iii) If data are insufficient to perform BMC modeling then the AEGL Program uses the highest dose that did not cause lethality in the experiment. I don't know how you define LCLo but assume it is a dose that causes some lethality. This is too high.

26) Table 4.2.1 Typical Uncertainty Factor Ranges and Appendix D – Put a footnote in the table that the preferred UFs are justified by the analysis done in Appendix D. They do not seem to be justified by using individual UFs.
27) Section 4.1 Application of Uncertainty Factors. You probably covered it in the weight of evidence approach but you should mention that after you derive the IDLH using your paradigm you should compare the value with known human data. If your

IDLH is at a level that humans can tolerate well in chamber studies, the UFs are too high and should be adjusted.

28) 68 3 – As justification for reducing the UF because the study was done on a susceptible population you might also mention asthmatics in the case of irritants.

29) 70 3 – You state you do not assign a value to each area of uncertainty. If you do not, then how is the NIOSH UF derived. See comment 25) a) above. Using a preferred UF of 30 when going from an LC50 in an animal to an IDLH does explicitly consider all appropriate UFs. If you have data to say a total UF of 100 is too high then you should use that information to lower the total UF. However, a UF of 30 to predict an IDLH from an LC50 value assigns a 1 to at least one of the UFs in the chain (e.g 1) a factor of 3 to predict the non-lethal level; 2) a factor of 3 to predict the threshold for irreversible effects from the threshold for lethality; 3) a factor of 3 to extrapolate to humans from animals; and 4) a factor of 3 to account for human variability). If you do not specify the UFs used and the rationale, you lose transparency. If anyone wants to revise the IDLH in the future when more data may become available, they will not have the benefit of your rationale.

30) 70 8 – You state why the IDLH may be higher than an AEGL or an ERPG. Your rationale is well taken and certainly true in many cases. However, as you point out, asthmatics, or other populations, might have to be considered in which case all values would essentially be the same. The important point is to assess each chemical individually.

31) Appendix A – Example of the Derivation of an IDLH Value

   a) This seems a concise presentation of the data and the methodology used to derive the IDLH. The major comment is that a rationale needs to be given for the use of the total UF of 30. Appendix D works to document this but needs more detail (see comments below). A more detailed presentation and discussion in Appendix D would help greatly in this justification.

   b) There is no rationale for using a total UF of 30 to derive the IDLH from the LC50. Table 4.2.1 presents a typical UF range for LC50 data as 10 to 100. Why not use 10? 100?

   c) You might also note that the Bodgdanfy study would give something like 230 ppm for the IDLH (1000 ppm 6 hour exposure for reversible effects scaled back to 30 minutes = 2289 ppm; UFs of 3 to go from animal to human and 3 for human variability). This would lend support to your analysis to say it is at least protective. In fact this could justify your use of a total UF of 30. This type of discussion should be part of your weight of evidence analysis.

   d) The AEGL for vinyl acetate states *"Groups of 5 male and 5 female Sprague-Dawley rats or CD 1 mice were exposed 6 hours/day, 5 days/ week for 4 weeks to 0, 50, 150, 500, or 1000 ppm VA (Owen, 1979a; b). The 50 ppm exposure was increased to 1500 ppm on day 10 (rats) or day 8 (mouse) due to a lack of marked clinical effects in the 1000 ppm groups. Animals were exposed in a stainless steel and glass dynamic inhalation exposure chamber, with chamber concentrations measured every 15 minutes by gas chromatography. Mean measured concentrations (ppm; v/v) for the rat and mouse exposures were 51.3, 150.5, 497.6, 1000.2, and 1488.5 (rats) or 1488.7 (mouse). All animals survived treatment."* The fact that mice could survive multiple exposures to 1,000 ppm for

6 hours calls into question the Smyth and Carpenter study. In fact the AEGL document notes *"Because the exposure concentrations in the Smyth and Carpenter (1973) study were not measured, but corrected using a curve based on gas chromatographic analysis of calculated concentrations, it is possible that the exposure concentrations reported are not accurate. Therefore, these data were not used for derivation of the AEGL-3."* when discussing why the lethality data may be suspect for AEGL-3 derivation.

e) The question of how much analysis you need to do is a delicate balance between your budget and the need to develop a reasonable output level. It is interesting to note that the approach in the NIOSH document and the AEGL document give essentially the same value (100 vs 230 ppm) and reinforce the approach taken to develop the IDLH.

f) Regardless, more work should be done on Appendix D to better document why you arrived at your conclusions. This will probably be critical to justifying your choice of the development of the total UF.

32) Appendix D – Analyses Supporting the Development of Uncertainty Factor Approach. This is an important analysis that many in the community that assess chemicals for short duration exposure risks would welcome. It should be published in detail and in a peer reviewed journal. That would lend credibility to the analysis. As it stands, Appendix D cannot be reviewed because so many details of the analysis are not presented. The following are some general observations.

a) Approach One:

i) 112 17 – For LC50 duration adjustments you mention using the chemical specific n where available but do not mention what methodology you used when n is unknown. It should be the default you mention other places in the document. The value of n should be 1 when extrapolating from <30 minutes to 30 minutes and 3 when extrapolating from exposures >30 minutes to 30 minutes.

ii) 112 17-19 – You use a value of n for human effects other than lethality for time corrections. Actually, as the severity of an irritant effect diminishes to tolerable irritation, the value of n is expected to increase until it reaches infinity. In this limiting case, as long as you stay at a low level of irritation, adaptation occurs and the concentration does not change. The other effect mentioned is for CNS depression. Again, the value of n will be much greater than 1 for this effect. Typically CNS depression is a function of the level in the blood. Below that level it does not occur. Thus, once you reach equilibrium, duration of exposure is not a factor.

iii) 112 23-26 – You talk about effect levels from secondary sources arrayed by concentration, duration, and their product.

(1) If possible original sources should be used. Many times secondary sources give a value but you cannot find the original reference or the original reference is interpreted differently for the purpose you wish.

(2) Looking at the ct product is not valid for the points raised above about irritants and CNS depressants.

(3) The chemicals assessed in your analysis should be in a table as well as the animal data and human effect. Citations for each value should be

presented. Without this information, the reader cannot evaluate what was done nor have confidence in the analysis.

(4) What does "available effect levels in humans" mean? What effects at what levels? Was the determination made from chamber studies that are very reliable or from case reports where the exposure parameters are very uncertain with regard to duration and exposure? From line 12 on this page you are presumably estimating human lethality thresholds. Human chamber studies do not usually approach these levels. Use of chamber studies would give too low a value. If case reports, these are rarely sufficient to provide reliable data.

(5) Table D.1 – Without an understanding of how the LOEL and LCLO for humans were derived, the meaning of this analysis is unclear. Also, these two terms need to be defined precisely. As stated they are confusing. If the LOEL is the lowest effect level and was a non-lethal effect from a human chamber study then you have a better basis for the "preferred" total UF of 30 from an LC 50 (Table 4.2.1). Presentation of the basis for the LOEL determination can only help your case and further the science by allowing others to see your rationale.

b) Approach Two: Similar comments to Approach One.