National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances

December 10-12, 2003

Final Meeting-31 Highlights

La Mansion Del Rio
San Antonio, Texas

INTRODUCTION

Mr. Eric Stephens, Director of the Air Force Institute for Operational Health (AFIOH) welcomed the group to San Antonio and presented an overview of the AFOIH mission and the relevance of the AEGL process (Attachment 1). Mr. George Irving of Core 6 Solutions also welcomed the group and explained meeting logistics.

Ernie Falke announced that the AEGL public internet site should be up by January 5, 2004. The site will include proposed, interim, and final AEGL values, and .pdf files of the final documents; these files will be provided by the National Academy of Sciences and will be posted on the site. Ernie Falke also introduced Marquea King, a toxicologist on the EPA staff who is now working with the AEGL program.

The draft NAC/AEGL-30 meeting highlights were reviewed. Bob Benson pointed out that text was missing from the carbon monoxide discussion. Several committee members were concerned that no discussion was presented in the meeting summary text explaining the relationship of derived AEGL values for styrene, propane, and butane to the Lower Explosive Limit (LEL); explanation had only been included in the table footnotes. It was decided that the meeting highlights should be revised to include the LEL explanation in the text, while also maintaining the table footnotes. George Alexeeff pointed out that the AEGL-1 for propane was based on a NOAEL for vertigo; this needs to be added to the meeting summary. Marquea King explained that during NAC/AEGL-30, the AEGL-1 values for acetone cyanohydrin were not rounded correctly (AEGL-1 values were obtained by doubling the former AEGL-1 values after removing the modifying factor). The correct values should be 2.1 ppm (instead of 2.2 ppm) for the 10- and 30-min values and 0.69 ppm (instead of 0.70 ppm) for the 8-hour value. This modification was approved unanimously by a voice vote. A motion was made by John Hinz and seconded by Richard Thomas to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-30 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail.

The highlights of the NAC/AEGL-31 meeting are summarized below along with the Meeting Agenda (Attachment 2) and the Attendee List (Attachment 3). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-31 Agenda.

RESPONSES TO *FEDERAL REGISTER* COMMENTS ON THE PROPOSED AEGL VALUES

Comments from the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for ammonia, xylenes, and methyl ethyl ketone were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

Ammonia (CAS No. 7664-41-7)

Chemical Manager: Larry Gephart, ExxonMobil
Staff Scientist: Kowetha Davidson, ORNL

Comments were received from William C. Herz (Director of Scientific Programs, The Fertilizer Institute (TFI)), Mary Lee Hultin (Michigan Department of Environmental Quality), George Alexeeff, and John Morawetz. TFI commented on AEGL-1, -2, and -3 values; comments concerned the consistency of points of departure with the AEGL definitions, over-application of uncertainty factors (UF), time-scaling to 4- and 8-hour exposure durations, and potential for incorrect interpretation and regulatory misuse of AEGLs. Dr. Hultin commented that points of departure appeared to be based on appropriate science; however, concern was expressed regarding the selection of the intraspecies UF of only 1. Dr. Alexeeff and Mr. Morawetz both expressed concern regarding AEGL-2 and AEGL-3 values and the use of an intraspecies UF on 1. Kowetha Davidson responded to the scientific issues raised by these comments (Attachment 4). Dr. William Herz (Director of Scientific Programs for The Fertilizer Institute) also participated in the discussion and thanked the NAC for their thorough consideration of the comments. Dr. Davidson then proposed revising the AEGL-1 values (Attachment 5) from 25 ppm at all time points to 50 ppm at all time points based on moderate irritation in humans. After considerable discussion, a motion was made by Nancy Kim and seconded by Tom Hornshaw to adopt AEGL-1 values of 30 ppm for all time points based on very mild irritation in humans exposed to ammonia for 10 minutes. The motion passed (YES: 15; NO: 0; ABSTAIN: 3) (Appendix B). A motion was then made by Ernest Falke and seconded by George Rodgers to have no further discussion regarding AEGL-2 or AEGL-3 and to elevate the ammonia TSD to interim status. The motion passed (YES: 16; NO: 1; ABSTAIN: 0) (Appendix B).

SUMMARY OF INTERIM AEGL VALUES FOR AMMONIA [ppm (mg/m^3)]							
Classification	Exposure Duration						Endpoint (Reference)
	5 min	10 min	30 min	1 hour	4 hours	8 hours	
AEGL-1 (Nondisabling)	30 (20)	30 (20)	30 (20)	30 (20)	30 (20)	30 (20)	Very mild irritation (MacEwen et al., 1970); Verberk, 1977
AEGL-2 (Disabling)	380 (266)	270 (189)	160 (112)	110 (77)	110 (77)	110 (77)	Irritation: eyes and throat; urge to cough (Verberk, 1977)
AEGL-3 (Lethal)	3800 (2657)	2700 (1890)	1600 (1119)	1100 (769)	550 (385)	390 (273)	Lethality (Kapeghian et al., 1982; MacEwen and Vernot, 1972)

Xylenes (CAS No. 1330-20-7)

Chemical Manager: Bob Benson, EPA
Staff Scientist: Claudia Troxel, ORNL

Comments were received from George Alexeeff, United Auto Workers (UAW) International Union, Clean Channel Association, Michigan Department of Environmental Quality (DEQ), and The American Chemistry Council (ACC). Dr. Alexeeff's comments suggested revising AEGL-1, -2, and -3 derivation descriptions to improve clarity. The UAW comments also concerned clarity in the derivation of AEGL-1 and AEGL-2 values, in addition to health effects noted at AEGL-2 and AEGL-3 concentrations being consistent with the AEGL definitions. The Clean Channel Association commented on needed notation when AEGL values approach the Lower Explosive Limit (LEL). The Michigan DEQ and the ACC both commented on the need to more thoroughly explain why separate AEGL values were not derived for individual xylene isomers. Claudia Troxel responded to issues raised by these comments (Attachment 6) and provided the committee with a revised text of the Summary and derivation sections of the TSD (Attachment 7). Dr. Troxel then discussed using PBPK modeling to refine the derived AEGL values (Attachment 8), pointing out that there is a flaw in the current TSD in that the assumption is made that a human and rat exposed to the same external xylene concentration will have the same internal dose. However, the rat will actually experience a greater xylene dose due blood: air partitioning and greater ventilation rate. Discussion then focused on whether to use modeling as support for values derived by SOP methodologies or to derive values based on modeling. After considerable discussion, a motion was made by Ernest Falke and seconded by Richard Thomas to accept AEGL-2 values of 1100 ppm for 10-min, 600 ppm for 30-min, and 400 ppm for 1-, 4-, and 8-hours based on PBPK modeling suggesting that values are below the threshold for CNS depression at 2 hours (Carpenter et al., 1975). Values were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 14; NO: 1; ABSTAIN: 1) (Appendix C). A motion was then made by Bob Benson and seconded by Ernest Falke to accept AEGL-3 values of 3300 ppm for 10-min, 1700 ppm for 30-min, and 1100 ppm for 1-, 4-, and 8-

hours based on PBPK modeling with the endpoint of no lethality in rats exposed for 4 hours. Values again were based on exposure at 50W of work for 10 and 30 minutes and 1 hour, and then held constant for the 4- and 8-hour time points because it was assumed that it is unlikely that any individual could maintain 50W work for 4 to 8 hours. An intraspecies UF of 3 was applied. The motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix C). It was decided to pass the xylene values, but it was agreed that xylenes could come back to the committee if refinements on the PBPK model need to be made, particularly regarding the physiological parameters used for work.

Summary of Proposed AEGL Values for Xylenes (ppm)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	**130**	**130**	**130**	**130**	**130**	**Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 minutes (Hastings et al., 1986)**
AEGL–2 (Disabling)	**1100**	**600**	**400**	**400**	**400**	**Rats exposed to 1300 ppm mixed xylenes for 4 hours exhibited poor coordination (Carpenter et al., 1975)**
AEGL–3 (Lethal)	**3300**	**1700**	**1100**	**1100**	**1100**	**Rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery (Carpenter et al., 1975)**

Methyl Ethyl Ketone (CAS No. 79-93-3)

Staff Scientist: Sylvia Talmage, ORNL
Chemical manager: Bill Bress, ASTHO

Sylvia Talmage presented brief responses to comments to the Federal Register made by George Alexeeff, John Morawetz, the Michigan Department of Environmental Quality, and the Clean Channel Association (Attachment 9). New data, published since the development of AEGL values for methyl ethyl ketone (MEK) in December, 2001 and relevant to development of AEGL-1 values, were then discussed (Attachment 10). Based on three recent, well-conducted studies (Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002) and the previously considered study of Dick et al. (1992), in which no irritation was reported at 200 ppm in healthy subjects, including subjects with self-reported multiple chemical sensitivity, the AEGL-1 was raised from 100 to 200 ppm. The motion to change the value was made by Loren Koller and seconded by Ernest Falke. The motion passed (YES:9 ; NO :3; ABSTAIN: 5) (Appendix D).

Prior to the meeting, a NAC member raised the question of whether the constant AEGL-2 value of 1700 ppm across time was realistic based on the fact that MEK reaches equilibrium in the blood fairly rapidly. The 1700 ppm value had been based on a 6 hr/day subchronic study with rats (Cavender et al. 1983). The endpoint was the threshold for narcosis. Several options were presented for time scaling. The NAC decided to time-scale the 1700 ppm concentration back to 10 minutes using the default value of n = 3. The 8-hour value was kept at 1700 ppm. The motion was made by Steve Barbee and seconded by John Hinz to time scale the values back to 10 minutes. The motion passed (YES: 13 ; NO: 0 ; ABSTAIN: 4) (Appendix D).

Sylvia Talmage then reported that the AEGL-3 10- and 30-minute value of 10,000 ppm had been based on a projected rather than a measured concentration (Hansen et al. 1992). Because two additional studies supported the derived value (Klimisch 1988; Zakhari 1977), she suggested keeping the value, but revising the basis. The suggestion was accepted by voice vote. A motion was made by Loren Koller and seconded by John Hinz to elevate methyl ethyl ketone to interim status. The motion passed (Appendix D).

Summary of Interim AEGL Values for Methyl Ethyl Ketone

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm	NOAEL for subjective symptoms - humans (Dick et al. 1992; Shibata et al. 2002; Muttray et al. 2002; Seeber et al. 2002)
AEGL–2	4900 ppm*	3400 ppm*	1700 ppm	1700 ppm	1700 ppm	Threshold for narcosis - rats (Cavender et al. 1983)
AEGL–3	see below [a]#	see below [a]#	4000 ppm[b]*	2500 ppm[b]*	2500 ppm[b]*	Threshold for lethality - rat, mouse (Klimisch 1988; Zakhari 1977; La Belle and Brieger 1955)

[a]Based on Klimisch (1988); Zakhari (1977).

[b]Based on La Belle and Brieger (1955).

*: Concentrations are higher than 1/10 of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

#: The AEGL-3 value of 10,000 ppm (29,300 mg/m^3) for 10 and 30 minutes is higher than 50% of the lower explosive limit of methyl ethyl ketone in air (1.8% = 18,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

REVISIT OF CHEMICALS WITH SPECIFIC ISSUES

Acrylic Acid (CAS No. 79-10-7)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Peter Griem, FOBIG

Ernest Falke, Chemical Manager, explained a discrepancy between interim AEGL-2 values approved by the NAC and AEGL-2 values presented to the COT subcommittee (Attachment 11). This discrepancy resulted because the interim AEGL-2 values approved by the NAC were based on olfactory epithelial histopathology observed in monkeys and rats exposed to 75 ppm acrylic acid for *3 hours*, and the values presented to the COT subcommittee were based on similar histopathology noted in monkeys and rats exposed to 75 ppm for *6 hours*. After considerable discussion, a motion was made by Bob Benson and seconded by Loren Koller to reaffirm the AEGL-2 values based on the 3 hour point of departure and to revise the rationale to include concern about irreversibility of the histopathological lesions at the 6 hour time point. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix E).

Uranium Hexafluoride (CAS No. 7783-81-5)

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Cheryl Bast, ORNL

George Rusch, Chemical Manager, explained a discrepancy between interim AEGL-3 values approved by the NAC and AEGL-3 values presented to the COT subcommittee (Attachment 12). This discrepancy resulted because the interim AEGL-3 values utilized a time-scaling exponent 'n' of 0.66, derived from rat lethality data ranging from 2- to 60-min, and the AEGL-3 values presented to the COT subcommittee utilized an n=1 (0.66 value rounded up). Using n=0.66 yielded 10- and 30-minute AEGL-3 values for uranium hexafluoride where exposure to HF alone approached the hydrogen fluoride AEGL-3 values. (Uranium hexafluoride hydrolyzes to hydrogen fluoride and uranyl oxyfluoride, so exposure to UF6 may actually represent an exposure to both hydrolysis products). Therefore, a proposal was made to utilize an 'n' of 1 (rounded up from 0.66) to scale AEGL-3 values across time. This provides more protective 10- and 30-minute AEGL-3 values. The 4- and 8-hour AEGL-3 values are slightly increased, but still considered protective. Also, the use of an 'n' of 1 for extrapolating from 1-hr to 4- and 8-hr is consistent with the NAC Standing Operating Procedures (SOP) default approach. A motion was made by George Alexeeff and seconded by George Rodgers to adopt AEGL-3 values of 220 mg/m^3 for 10-min, 72 mg/m^3 for 30-min, 36 mg/m^3 for 1-hr, 9.0 mg/m^3 for 4-hr, and 4.5 mg/m^3 for 8-hr. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix F).

REVIEW of PRIORITY CHEMICALS

Hydrogen Iodide (CAS No. 10034-85-2)

Staff Scientist: Sylvia Talmage, ORNL
Chemical manager: Ernie Falke, U.S. EPA

Sylvia Talmage discussed the poor database for hydrogen iodide (Attachment 13). In the absence of inhalation data for derivation of AEGL values for hydrogen iodide, the options were to either not derive values or base the values on the most chemically similar hydrogen halide, hydrogen bromide. Richard Niemeier stated that there is a need for AEGL values for hydrogen iodide. A motion was made by Richard Niemier and seconded by John Hinz to adopt the hydrogen bromide values as the values for hydrogen iodide, and to combine both chemicals into one document, with a clear presentation of the fact that data are unavailable for hydrogen iodide, and, in the absence of data, the values for hydrogen bromide should be consulted. The motion passed (YES: 12; NO: 5; ABSTAIN: 0) (Appendix G).

Summary of AEGL Values for Hydrogen Bromide/Hydrogen Iodide[a]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm	Nose irritation in humans (CT Dept. Health 1955)
AEGL–2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Based on analogy with hydrogen chloride
AEGL–3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm	Threshold for lethality - rat (MacEwen and Vernot 1972)

[a] These values were derived based on empirical human and animal data for hydrogen bromide and other hydrogen halides. In the absence of inhalation data for hydrogen iodide, the values for hydrogen bromide should be consulted. Based on structure-activity relationships for the hydrogen halides, it is believed that hydrogen iodide is less toxic than hydrogen bromide. Therefore, application of the hydrogen bromide values for hydrogen iodide is conservative.

Sulfur Dichloride (CAS No. 10545-99-0)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Kowetha Davidson, ORNL

Kowetha Davidson presented information explaining that there are no human or animal data available to derive AEGL values for sulfur dichloride (Attachment 14). The chemical was placed in holding status (Appendix H).

Sulfur Chloride (CAS No. 10025-67-9)

Chemical Manager: Ernest Falke, U.S. EPA

Staff Scientist: Kowetha Davidson, ORNL

Kowetha Davidson reviewed the available data for sulfur chloride (Attachment 15). Data are limited to one rat study (Bomhard et al., 2000). After discussion, the chemical was placed in holding status (Appendix H), and an attempt will made to contact the study author to determine if more experimental detail can be obtained.

Chloroacetyl Chloride (CAS No. 79-04-9) and Dichloroacetyl Chloride (CAS No. 79-36-7)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on chloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). The proposed AEGL-1 values were based on mild eye irritation in rats exposed to 1 ppm chloroacetyl chloride for 6 hours (Dow, 1982). Intraspecies and interspecies UFs of 3 each (total UF = 10) were proposed because eye conjunctivitis due to local irritation is not expected to vary greatly between or within species. The proposed AEGL-1 value of 0.08 ppm was kept constant at all time points because mild irritant effects do not vary greatly over time.

The proposed AEGL-2 values were based on eye lacrimation and squinting (impaired ability to escape) in rats exposed to 32 ppm chloroacetyl chloride for 1 hour (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 10 was proposed because data suggest humans are more susceptible to lacrimation than animals. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed, except that the 4-hour value should be adopted as the 8-hour value because time scaling yields an 8-hour AEGL-2 value approaching the AEGL-1 value. Proposed AEGL-2 values were 1.9 ppm for 10-min, 1.3 ppm for 30-min, 1.1 ppm for 1-hour, and 0.27 ppm for 4- and 8-hours.

The proposed AEGL-3 values are based on an estimated lethality threshold of 215 ppm in rats (1/3 of the 1-hr rat LC_{50} value) (Dow, 1986). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 3 was proposed because rat and mouse lethality studies suggest a steep concentration-response curve at concentrations within a factor of 2-3. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. Proposed AEGL-3 values were 39 ppm for 10-min, 27 ppm for 30-min, 21 ppm for 1-hour, 5.4 ppm for 4-hours, and 2.7 ppm for 8-hours.

After much discussion, a motion was made by John Hinz and seconded by Bob Benson to accept the AEGL-1 values as proposed (0.08 ppm for all time periods). The motion did not pass (YES: 11; NO: 6; ABSTAIN: 1) (Appendix I). A motion was then made by George Alexeeff and seconded by Richard Niemier to adopt the AEGL-1 values as proposed with a modifying factor of 2 applied (0.04 ppm for all time points. This motion passed (YES: 11; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-2 values of 2.9 ppm for 10-min, 2.0 ppm for 30-min, 1.6 ppm for 1-hour, 0.40 ppm for 4-

hours, and 0.20 ppm for 8-hours. The point of departure is that proposed above (32 ppm, 1-hr); however, inter- and intraspecies UFs of 3 each are applied and a MF of 2 (LOAEL to NOAEL) is also applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 10; NO: 4; ABSTAIN: 3) (Appendix I). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-3 values of 95 ppm for 10-min, 66 ppm for 30-min, 50 ppm for 1-hour, 13 ppm for 4-hours, and 6.5 ppm for 8-hours. The point of departure is the highest concentration (522 ppm) causing no deaths in rats exposed for 1 hour (Dow, 1986); inter- and intraspecies UFs of 3 each are applied. Time scaling using n=3 for <1 hour and n=1 for >1 hour was proposed. The motion passed (YES: 13; NO: 2; ABSTAIN: 3) (Appendix I).

Summary of AEGL Values for Chloroacetyl chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	Eye irritation in rats (Dow, 1986)
AEGL–2	2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.40 ppm	Lacrimation and squinting in rats (Dow, 1986)
AEGL–3	95 ppm	66 ppm	50 ppm	13 ppm	6.5 ppm	Highest concentration causing No deaths in rats (Dow, 1986)

The chemical review on dichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1 values were not recommended due to insufficient data.

The proposed AEGL-2 values were based on coughing and notable discomfort in workers exposed to 1.6 ppm dichloroacetyl chloride for an estimated duration of 10 min (Dahlberg and Myrin, 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, because coughing and notable discomfort is not likely to be significantly worst in the general population than in repeatedly exposed workers. Time scaling using n=1 scaling from 10-min to 30 min and maintaining the same value from 30-min to 8-hr was proposed, because scaling to 1-, 4-, and 8-hour time periods yielded concentrations below those recognized by workers. Proposed AEGL-2 values were 0.53 ppm for 10-min, and 0.18 ppm for 30-min, 1-, 4-, and 8-hours.

The proposed AEGL-3 values are based on an estimated 4-hour lethality threshold of 500 ppm in rats (Smyth et al., 1951). An intraspecies UF of 10 because the cause of death in the key study was unknown and variability among humans cannot be reliably estimated. An interspecies UF of 10 was proposed because only one species was tested and the cause of death was unknown. Time scaling using n=3 for <4 hours and n=1 for >4 hours was proposed, except that the 30-min value should be adopted as the 10-min value. Proposed AEGL-3 values were 10 ppm for 10-min and 30-min, 7.9 ppm for 1-hour, 5.0 ppm for 4-hours, and 2.5 ppm for 8-hours.

After much discussion, a motion was made by Bob Benson and seconded by Loren Koller to not recommend AEGL-1 because of insufficient data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix J). A motion was then made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed. This motion did not pass. After considerable discussion concerning the relative toxicity of chloroacetyl chloride and dichloroacetyl chloride, a motion was made by George Alexeeff and seconded by Richard Thomas for AEGL-3 to combine the dichloroacetyl chloride TSD with the chloroacetyl chloride TSD, explain that dichloroacetyl chloride is less toxic than chloroacetyl chloride, and recommended adopting chloroacetyl chloride values for dichloroacetyl chloride. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J). A motion was then made by Steve Barbee and seconded by Bill Bress to adopt chloroacetyl chloride AEGL-2 values as the AEGL-2 values for dichloroacetyl chloride, and combining the TSDs as was done for AEGL-3. The motion passed (YES: 14; NO: 0; ABSTAIN: 2) (Appendix I). A motion was then made by Richard Thomas and seconded by Loren Koller to reopen the AEGL-1 discussion; this motion passed by a show of hands. A motion was then made by Ernest Falke and seconded by Loren Koller to adopt the chloroacetyl chloride AEGL-1 values as the AEGL-1 values for dichloroacetyl chloride and present in the combined TSD. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J).

Trichloroacetyl Chloride (CAS No. 76-02-8)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on trichloroacetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion was made by Richard Thomas and seconded by Ernest Falke to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix K).

Acetyl Chloride (CAS No. 75-36-5)

Chemical Manager: Steven Barbee, Arch Chemical
Staff Scientist: Sylvia Milanez, ORNL

The chemical review on acetyl chloride was presented by Sylvia Milanez (Attachment 16). AEGL-1, AEGL-2, and AEGL-3 values were not recommended due to insufficient data. A motion was made by Ernest Falke and seconded by Richard Thomas to not recommend AEGL-1, AEGL-2, or AEGL-3 values due to insufficient data and to include this information in the TSD for chloroacetyl chloride. The motion passed unanimously by a show of hands (Appendix L).

Tetrachloroethylene (CAS No. 127-18-4)

Staff Scientist: Claudia Troxel, ORNL
Chemical Manager: Bill Bress, ASTHO

Tetrachloroethylene will be discussed at a future meeting after modeling is completed.

Oleum (CAS No. 8014-95-7)
Sulfuric Acid (CAS No. 7664-93-9)
Sulfur Trioxide (Cas No. 7446-11-9)

Staff Scientist: Johan Schefferlie, Netherlands
Chemical Manager: Loren Koller

Johan Schefferlie presented a progress report on sulfuric acid, sulfur trioxide, and oleum (Attachment 17). These three chemicals will be presented together in one TSD and values will be derived only for sulfuric acid. This TSD will be presented at a future NAC meeting.

Methacrylonitrile (CAS No. 126-98-7)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rodgers

A brief history of the TSD and chemical review for methacrylonitrile was presented by Cheryl Bast (Attachment 18). The proposed AEGL-1 was based on transitory nasal, throat or ocular irritation in humans exposed to 2 ppm methacrylonitrile for 10 minutes (Pozzani et al., 1968). No uncertainty factor was applied to account for sensitive human populations because similar transitory irritation was noted in humans at 14 ppm. The 2 ppm concentration was held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure time points. This approach is considered appropriate since mild irritant effects generally do not vary greatly over time.

The proposed AEGL-2 was based on a 13-15% decrease in fetal body weight in rats exposed to 100 ppm methacrylonitrile 6 hours/day on gestation days 6-20 (Saillenfait et al., 1993). An uncertainty factor of 3 was applied to account for sensitive individuals. This uncertainty factor is considered sufficient because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN (the metabolically-liberated toxicant) but the magnitude of these differences does not appear to be great (NRC, 2002). An interspecies uncertainty factor of 3 was also applied, because use of the full uncertainty interspecies factor of 10, would yield AEGL-2 values that are not consistent with the total data set. For time scaling, an *n* of 3 was applied to extrapolate to the 30-minute, 1-hour, and 4-hour time periods, and an *n* of 1

was applied to extrapolate to the 8-hour time period. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 22 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hours, and 7.5 ppm for 8-hours.

The loss of consciousness, with no mortality noted, in rats exposed to 176 ppm for 3 hours was used as the basis of proposed AEGL-3 values (Pozzani et al., 1968). An uncertainty factor of 3 was applied to account for sensitive individuals, and interspecies uncertainty factor of 3 was also applied. Rationale for the UFs is the same as explained above for the AEGL-2 derivation. For time scaling, an *n* of 3 was applied to extrapolate to the 10-minute, 30-minute, 1-hour, and an n of 1 was used for extrapolation to the 4-hour time period. The 4-hour AEGL-3 value was also adopted as the 8-hour AEGL-3 value because time scaling would yield an 8-hour AEGL-3 value less that the 8-hour AEGL-2 value. The proposed AEGL-3 values were 32 ppm for 10-min and 30-min, 25 ppm for 1-hr, and 13 ppm for 4- and 8-hours.

After extensive discussion, a motion was made by George Rodgers and seconded by Loren Koller to accept the AEGL-3 values as presented. The motion passed (YES: 11; NO: 0; ABSTAIN: 3) (Appendix M). A motion was then made by Bob Benson and seconded by George Rodgers to derive AEGL-2 values by dividing AEGL-3 values by 2 (16 ppm for 10- and 30-min, 13 ppm for 1-hr, and 6.5 ppm for 4- and 8-hours). This approach is justified due to the relatively steep concentration-response curve, and dividing the AEGL-3 values by 3 (as per the SOP) for this chemical would yield AEGL-2 values in the range where only minor irritation was noted in humans. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M). A motion was then made by George Rodgers and seconded by Loren Koller to adopt AEGL-1 values of 2.0 ppm for 10-min and 30-min, as proposed, and 1.0 ppm for 1-hr, 4-hr, and 8-hr due to the lack of human data beyond 10-minutes and the potential for a systemic effect. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix M).

Summary of AEGL Values For Methacrylonitrile [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1	2.0 (5.5)	2.0 (5.5)	1.0 (2.8)	1.0 (2.8)	1.0 (2.8)	Transient nasal, throat, or ocular irritation in humans (Pozzani et al., 1968)
AEGL-2	16 (44)	16 (44)	13 (35)	6.5 (15)	6.5 (15)	AEGL-3 ÷ 2
AEGL-3	32 (88)	32 (88)	25 (69)	13 (36)	13 (36)	Loss of consciousness, no mortality in rats (Pozzani et al., 1968)

Benzonitrile (CAS No. 100-47-0)

Staff Scientist: Cheryl Bast, ORNL

Chemical Manager: George Rodgers

The chemical review for benzonitrile was presented by Cheryl Bast (Attachment 19).
The proposed AEGL-1 was based on irritation of extremities in rats exposed to 900 ppm for 1 hour (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was also applied to account for the sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute time period, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. Proposed AEGL-1 values were 19 ppm for 10- and 30-min, 15 ppm for 1-hr, 3.8 ppm for 4-hours, and 2.0 ppm for 8-hours.

The proposed AEGL-2 was based on labored breathing and poor coordination in rats exposed to 900 ppm for 3 hours (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. This intraspecies uncertainty factor of 3 is supported by the steep concentration-response curve, which implies little individual variability. A modifying factor of 2 was applied to account for the sparse data base and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value. Proposed AEGL-2 values were 27 ppm for 10- and 30-min, 22 ppm for 1-hr, 11 ppm for 4-hr, and 5.6 ppm for 8-hr.

The exposure of mice to 890 ppm for 2 hours resulting in 1/7 deaths in mice was used as the basis of the proposed AEGL-3 values (MacEwen and Vernot, 1974). An interspecies uncertainty factor of 3 was applied, and an uncertainty factor of 3 was also applied to account for sensitive individuals. Uncertainty factor justifications are as described above for AEGL-2. A modifying factor of 2 was applied to account for the use of an endpoint where 1 of 10 animals died, the sparse data base, and to protect against potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974). An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour, time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute value was adopted as the 10-minute value due to the added uncertainty of extrapolating from a 2-hour time point to 10-minutes. The proposed AEGL-3 values were 71 ppm for 10- and 30-min, 56 ppm for 1-hr, 23 ppm for 4-hr, and 11 ppm for 8-hr.

After discussion, a motion was made by Bob Benson and seconded by Ernest Falke to accept the AEGL-3 values as proposed except for the 10-min value which should be derived by time scaling per the SOP. Thus, the 10-min AEGL-3 value becomes 100 ppm. The motion passed (YES: 15; NO: 1; ABSTAIN: 0) (Appendix N). A motion was then made by George Rodgers and seconded by Bob Benson to accept the AEGL-2 values as proposed except for the 10-min value which

should be derived by time scaling per the SOP. Thus, the 10-min AEGL-2 value becomes 39 ppm. The motion passed (YES: 14; NO: 2; ABSTAIN: 0) (Appendix N). A motion was then made by Bob Benson and seconded by Ernest Falke not to recommended AEGL-1 values due to the lack of data. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix N).

Summary of AEGL Values for Benzonitrile						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	Insufficient data to derive AEGL-1 values
AEGL-2	39 (163)	27 (113)	22 (92)	12 (50)	5.5 (21)	Labored breathing, incoordination in rats (MacEwen and Vernot, 1974)
AEGL-3	100 (420)	71 (298)	56 (235)	23 (97)	11 (46)	14% death in mice (MacEwen and Vernot, 1974)

NR: Not Recommended.

Special Presentation

George Woodall presented information on a comparative survey of acute inhalation health reference values (Attachment 20).

Administrative Matters

The site and time of future meetings is as follows:

NAC/AEGL-32: April 19-21, 2004, Washington DC
NAC/AEGL-33: June 14-16, 2004, Netherlands
NAC/AEGL-34: September 21-23, 2004, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective chemical managers, staff scientists, and other contributors.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

Attachment 1. Overview of AFOIH
Attachment 2. NAC/AEGL-31 Meeting Agenda
Attachment 3. NAC/AEGL-31 Attendee List
Attachment 4. Response to Federal Register Comments for ammonia
Attachment 5. Proposed AEGL-1 revision for ammonia
Attachment 6. Response to Federal Register comments for xylenes
Attachment 7. Revised text for xylenes
Attachment 8. PBPK modeling for xylenes
Attachment 9. Response to Federal Register Comments for methyl ethyl ketone
Attachment 10. New AEGL-1 data for methyl ethyl ketone
Attachment 11. AEGL-2 issues for acrylic acid
Attachment 12. AEGL-3 time scaling issue for uranium hexafluoride
Attachment 13. Data Analysis of hydrogen iodide
Attachment 14. Data Analysis of sulfur dichloride
Attachment 15. Data Analysis of sulfur chloride
Attachment 16. Data Analysis of chloroacetyl chloride, dichloroacetyl chloride, trichloroacetyl chloride, and acetyl chloride
Attachment 17. Sulfuric acid, sulfur trioxide, and oleum progress report
Attachment 18. Data Analysis of methacrylonitrile
Attachment 19. Data Analysis of benzonitrile
Attachment 20. Comparative survey of acute inhalation health reference values

LIST OF APPENDICES

Appendix A. Final meeting highlights of NAC/AEGL-30
Appendix B. Ballot for ammonia
Appendix C. Ballot for xylenes
Appendix D. Ballot for methyl ethyl ketone
Appendix E. Ballot for acrylic acid
Appendix F. Ballot for uranium hexafluoride
Appendix G. Ballot for hydrogen iodide
Appendix H. Ballots for sulfur dichloride and sulfur chloride
Appendix I. Ballot for chloroacetyl chloride
Appendix J. Ballot for dichloroacetyl chloride
Appendix K. Ballot for trichloroacetyl chloride
Appendix L. Ballot for acetyl chloride
Appendix M. Ballot for methacrylonitrile
Appendix N. Ballot for benzonitrile

ATTACHMENT 1

U.S. AIR FORCE

AFIOH
Air Force Institute for Operational Health

PREVENT ANALYZE RESPOND
AFIOH

WELCOME NAC-AEGL!

AFIOH Overview Briefing

Dec 10, 2003

Mr. Eric Stephens
Director

AFIOH Mission

U.S. AIR FORCE

- Enhance Mission Effectiveness, Protect Health, Improve Readiness and Reduce Costs (Force Health Protection)
- Assess and Manage Risks (Radiological, Biological, Chemical & Operational)
- Risks to...
  - Human Health & Safety
  - Operational Performance
  - Environment

"Sustaining Readiness Through Healthy Communities since 1955"

U.S. AIR FORCE

Relevance

- DoD Health Affairs top priorities:
  - Provide a fit and healthy force
  - Build healthy communities
- AF/SG Doctrine:
  - Medical care in contingencies
  - Population based health care
  - Human performance
  - World health care

U.S. AIR FORCE

Mission Relevance
NAC-AEGL to AFIOH

- AEGL Chemicals in DOD Inventory
  - 74% (343) AEGL chems in HMIS
  - 35 AEGL chems found at restoration sites (ERPIMS)
  - 56 AEGL chems listed on Superfund
- Sample of AEGLs of particular interest to AF

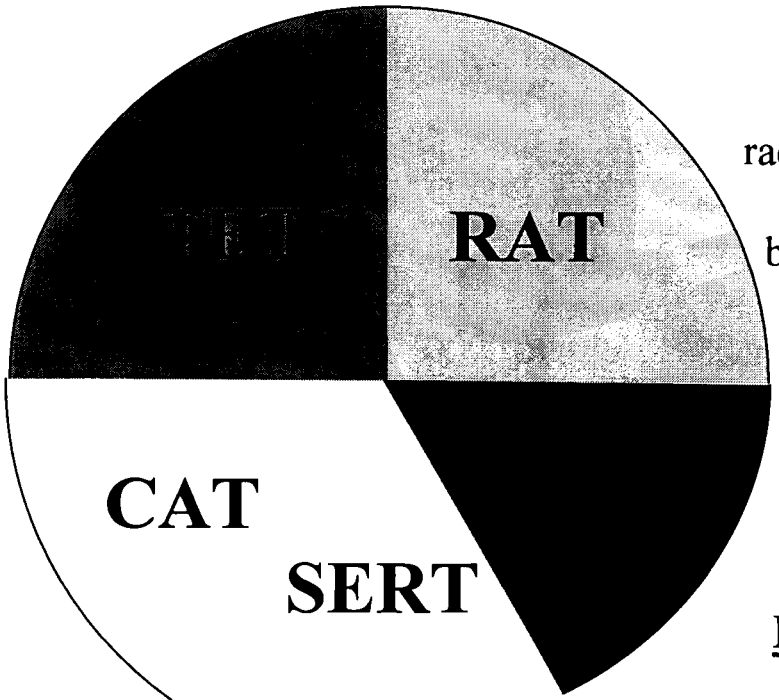
chem warfare agents	hydrogen chloride
hydrazines	oxides of nitrogen
CFC replacements	trichloroethylene
jet fuel	1,4-dioxane

AFIOH Readiness Capabilities

U.S. AIR FORCE

Theater Epidemiology Team (TET)

The Mission: Deployable disease and injury surveillance; threat assessments and countermeasure recommendations



Radiation Assessment Team (RAT)

The Mission: Response to radiation accidents/incidents; on-site health physics, bioenvironmental engineering, and occupational medicine

Chemical Assessment Team (CAT)

The Mission: Analysis of air, soil, and water; health, occupation and environmental on-site risk assessments

Smallpox Epidemiology Response Team (SERT)

The Mission: Deployable outbreak investigation team

Biological Augmentation Team (BAT)

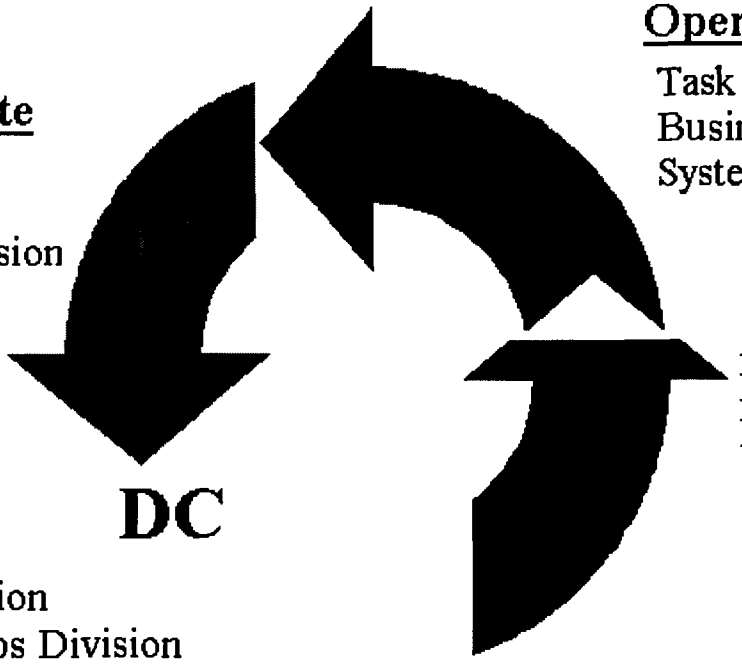
The Mission: Application of advanced molecular epidemiology techniques to rapidly identify diseases & microorganisms

AFIOH Reachback

U.S. AIR FORCE

Operations Directorate
Task Response Division
Business Division
Systems Division

Risk Analysis Directorate
Health & Safety Division
Risk Assessment Division
Environmental Analysis Division

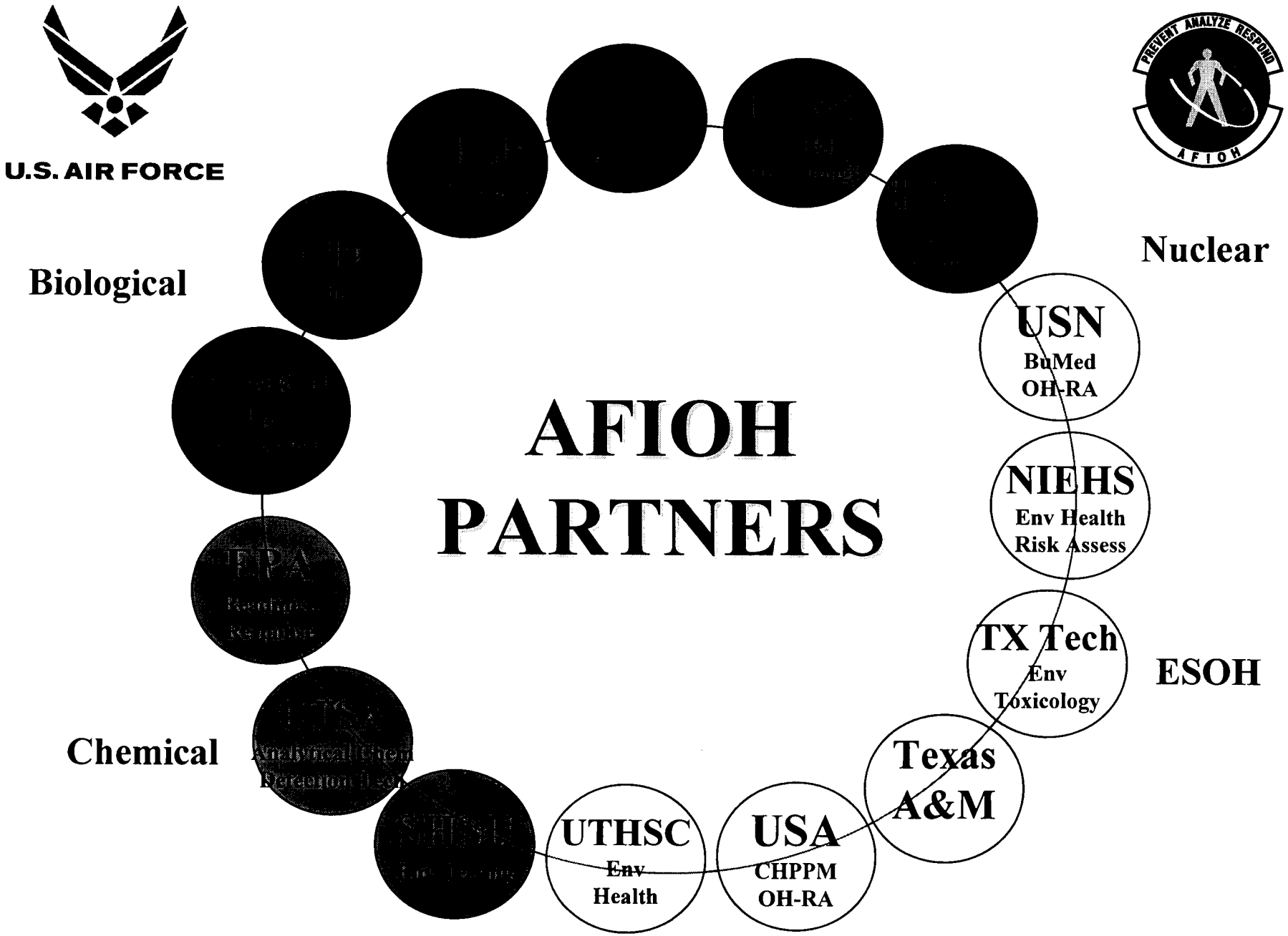


torate
Epidemiological Surveillance Division
Radiation Surveillance Division
Drug Testing Division
Chemistry Division

for Operational
Medicine Directorate
Operational Medicine Division
Military/Civilian Partnerships Division
Exercises, Training & Education Division

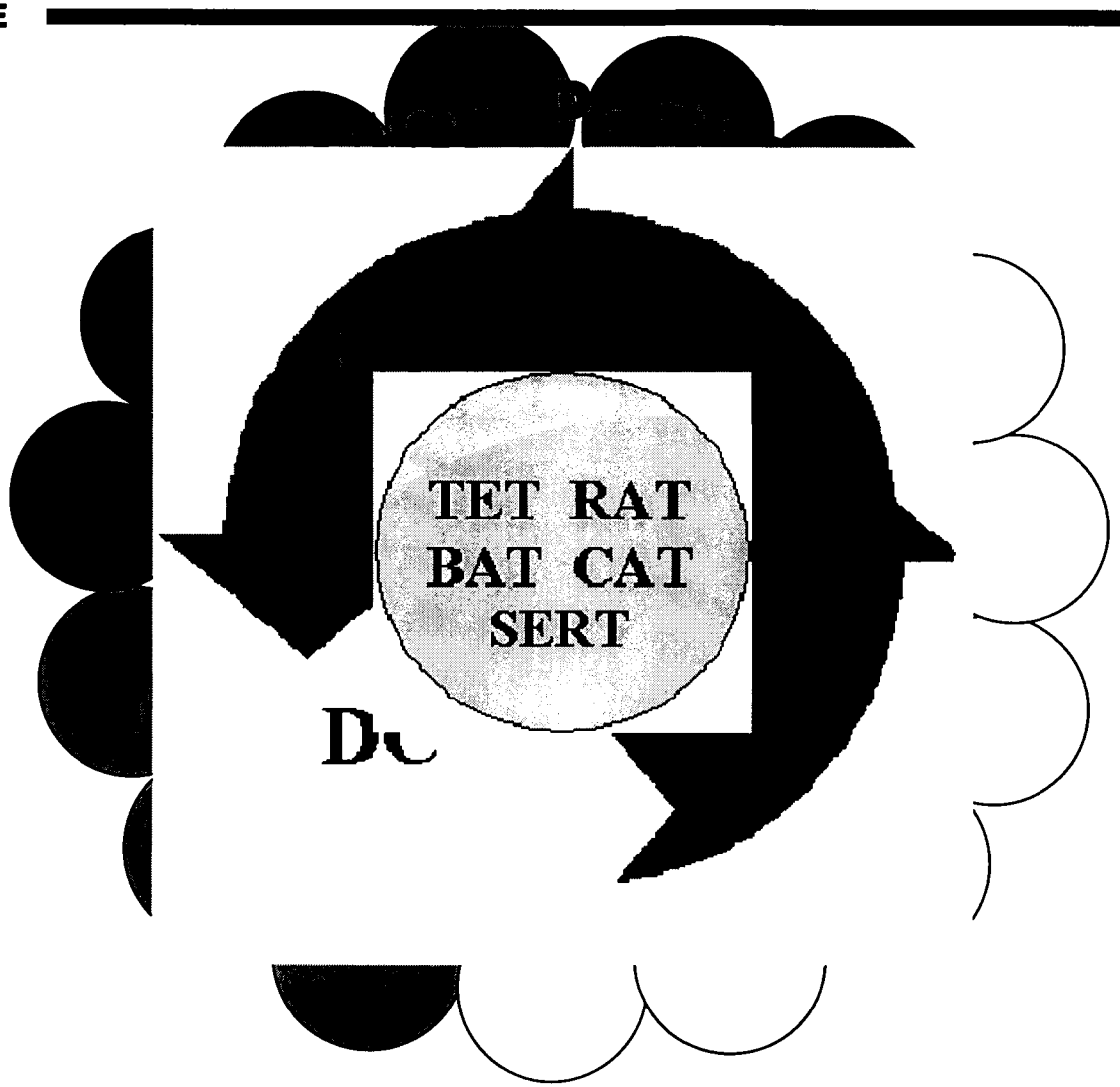
DC

Detachment 3, Kadena AB


U.S. AIR FORCE
PREVENT ANALYZE RESPOND
AFIOH
AFIOH
PARTNERS
Biological
Nuclear
Chemical
ESOH
USN
BuMed
OH-RA
NIEHS
Env Health
Risk Assess
TX Tech
Env
Toxicology
Texas
A&M
USA
CHPPM
OH-RA
UTHSC
Env
Health

U.S. AIR FORCE

Total Capability



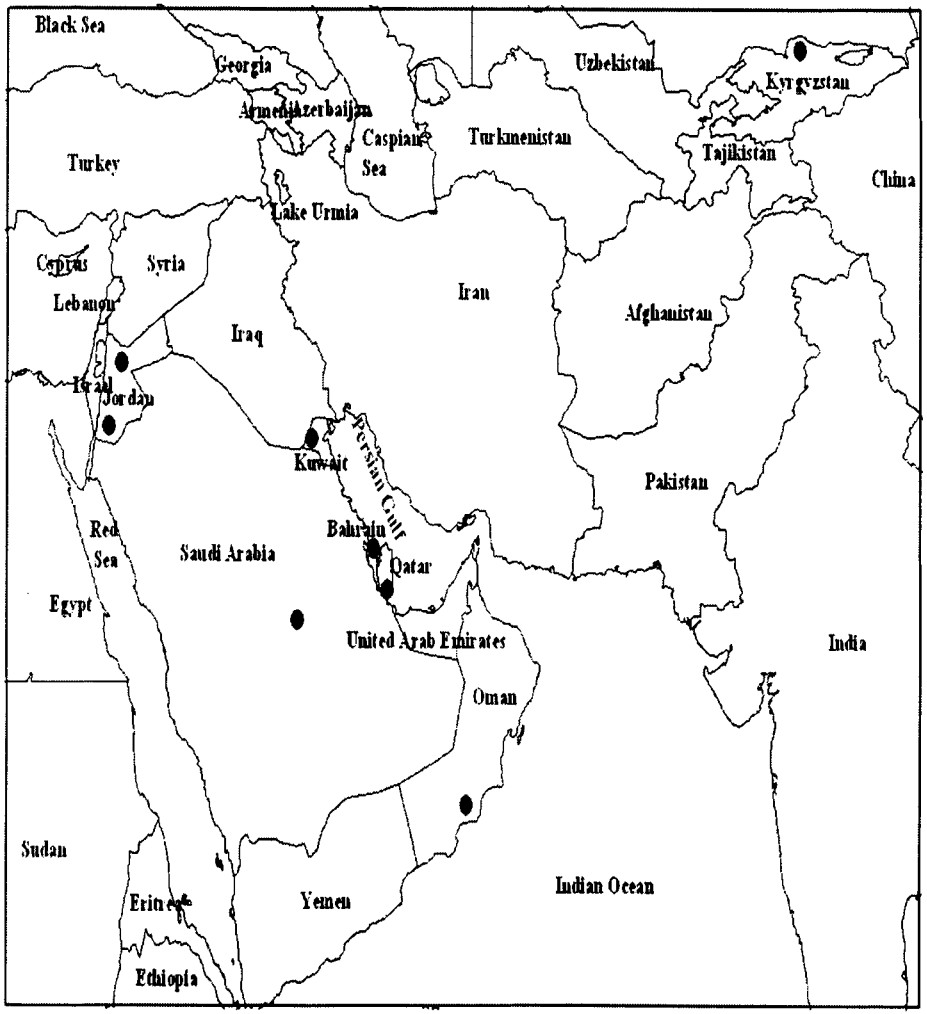
Diverse Manpower Mix

U.S. AIR FORCE

- Core competencies produced from a diverse mix of professionals and technicians
  - Toxicologists & Epidemiologists
  - Virologists & Microbiologists
  - Health Physicists & Chemists
  - Preventive, Aerospace & Occupational MDs
  - Industrial Hygienists & Ergonomists
  - Environmental, Chemical & Bioenvironmental Engineers
  - System & Program Managers

Staff Deployments

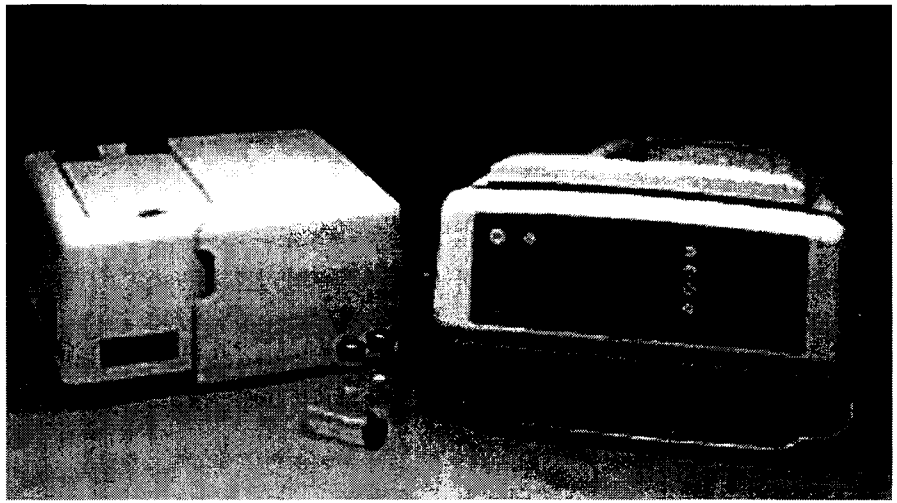
U.S. AIR FORCE

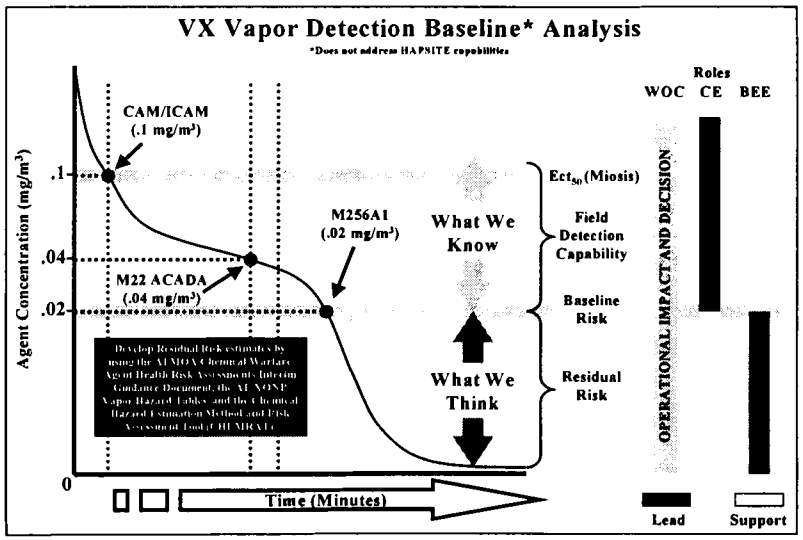


- 15 personnel - 7 countries
- 1 NCO, 4 airmen – Escort duty
- 3 PHOs – Preventive medicine
- 2 lab officers – BAT, AOR bio-detection training
- 1 BEE – NBC detection
- 1 Doc – Preventive medicine
- 1 Admin SNCO – Postal svc.

Chemical:
Warfare Agent Identification

U.S. AIR FORCE



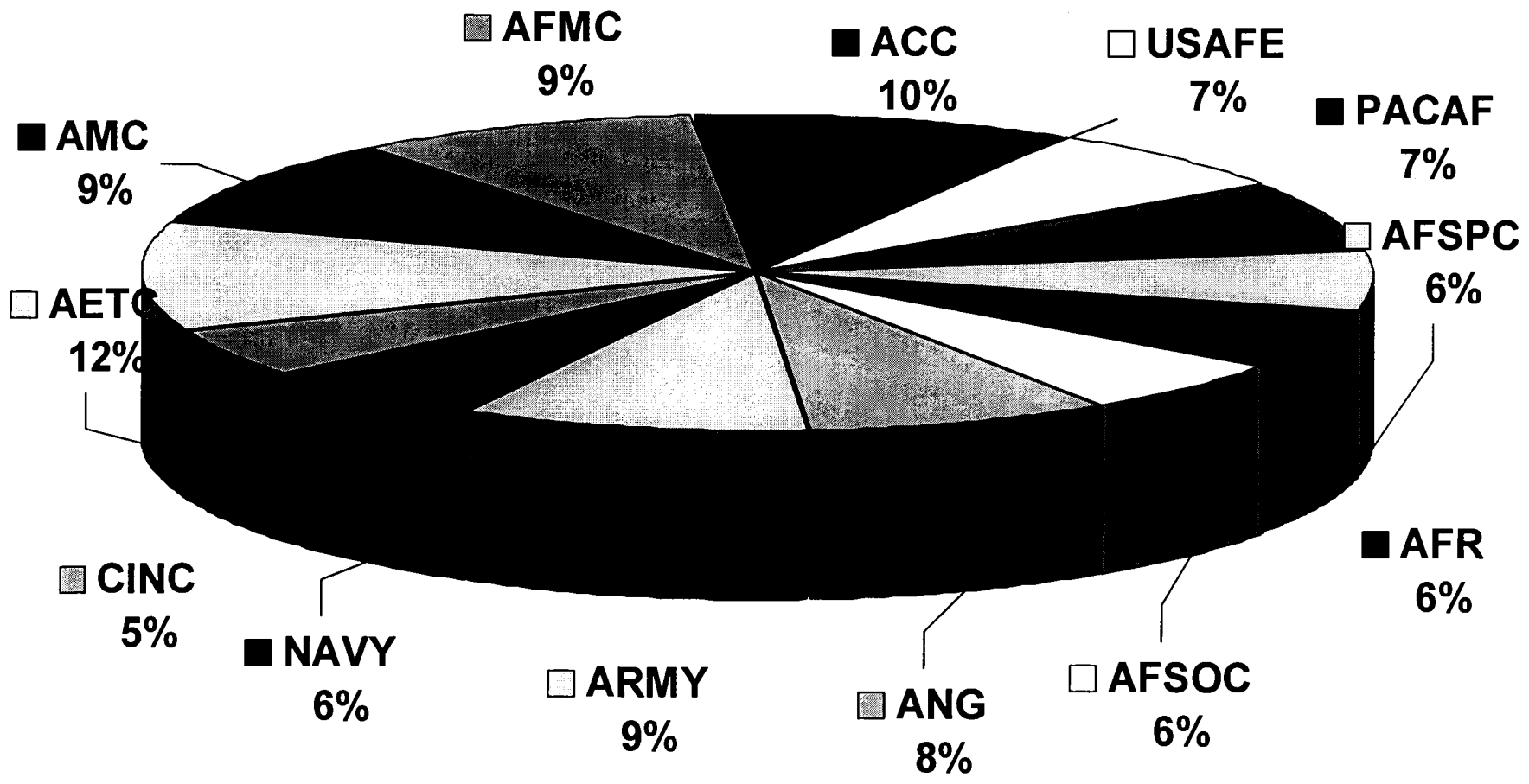


- Fielded COTS portable gas chromatograph/mass spectrometers to AOR
  - Identifies and quantifies Chemical Warfare Agents (CWAs)
  - Techniques used in CENTAF & USAFE
- Created AF Pamphlet for CWA health risk assessment
- Solidified reachback support for AOR analytical needs
- Partnering with CDC's Chemical Terrorism Laboratory Network
- DoD Triservice Lab WG

Customers
In-House Sample Analysis

U.S. AIR FORCE

Total Number = 2,000,000



U.S. AIR FORCE

AFIOH Summary
Products & Services

- **In-House Analysis (2M) + Environmental Exposures and Health Outcomes**
  - **Data** — **50,000,000**
- **Customer Studies**
  - **Information** — **2,000**
- **AF/DoD Databases/Reports**
  - **Knowledge** — **18**

U.S. AIR FORCE

AF Programs and Databases

- Master Radiation Exposure Registry
- Disease, Non-Battle Injury (DNBI)
- Hazardous Material Information System
- Air Emission Inventory
- Hearing Conservation Data Registry
- Suicide Events Surveillance
- AF Mortality Registry
- Alcohol and Drug Abuse

U.S. AIR FORCE

Goals

- **Readiness**
  - **Lighter, leaner, faster with better Reachback**
- **Customer Service**
  - **Meet our customers expectations…make commitments and keep them.**
- **People**
  - **Provide challenging work and an environment to excel.**

U.S. AIR FORCE

QUESTIONS?

Mr. Eric L. Stephens
Director
Air Force Institute for Operational Health
2513 Kennedy Circle
Brooks City-Base, TX 78235-5116
T: (210) 536-2003

"Sustaining Readiness
Through Healthy Communities since 1955"

ATTACHMENT 2

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-31
December 10-12, 2003

La Mansion Del Rio
San Antonio, Texas

AGENDA

Wednesday, December 10, 2003

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-30 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15	Revisit of Acrylic Acid (Ernest Falke/Peter Griem)
10:45	Revisit of Uranium Hexafluoride AEGL-3- Time scaling (George Rusch/Cheryl Bast)
11:15	Review of Disulfur dichloride and Sulfur dichloride (Ernest Falke/Kowetha Davidson)
11:45	Review of Hydrogen iodide (Ernest Falke/Sylvia Talmage)
12:15 p.m.	Lunch
1:15	Review of Chloroacetyl chloride (Steve Barbee/Sylvia Milanez)
3:00	Break
3:15	Review of Acetyl chloride, Dichloroacetyl chloride, and Trichloroacetylchloride (Steve Barbee/Bob Benson/Sylvia Milanez)
4:30	Revisit of Tetrachloroethylene (Bill Bress/Claudia Troxel)
5:30	Adjourn for the day

Thursday, December 11, 2003

8:00 a.m.	Review of Oleum, Sulfuric acid, and Sulfur trioxide (Loren Koller/Netherlands)
10:00	Break
10:15	Review of Methacrylonitrile (George Rodgers/Cheryl Bast)
11:15	Review of Benzonitrile (George Rodgers/Cheryl Bast)
12:15p.m.	Lunch
1:15	Discussion of Federal Register Public Comments (Ammonia, Bromine, Methyl ethyl ketone, Xylenes)
5:00	Adjourn for the day

Friday, December 12, 2003

8:00 a.m.	Review of Methyl Chloride (George Rodgers/Sylvia Talmage)
9:45 a.m.	Review of human health standards (G. Woodall)
10:00	Break
10:15	Review of Vinyl Acetate (Richard Thomas/Claudia Troxel)
11:45	Administrative matters
12:00 noon	Adjourn meeting

ATTACHMENT 3

NAC-AEGL #31

(National Advisory Committee for Acute Exposure Guidelines for Hazardous Substances)

San Antonio, TX

December 10-12, 2003

US AIR FORCE

Attendance

NAME	ORGANIZATION	Phone	FAX
Cheryl Bast	ORNL	865-574-7581	865-574-9888
Sylvia Talmage	ORNL	865-576-7758	"
Jim Holler	ATSDR	770-488-3358	—
George Woodall	EPA/ORD	919-541-3896	919-541-0245
Rick Niemeier	CDC/NIOSH	(513) 533-8388	(513) 533-8588
GEORGE CUSHMAC	DOT	202-366-4493	—
STEVEN BARBEE	ARCH CHEMICALS	203-229-2693	203-229-3543
Bill Bress	VA DOH, ASTHO	802-863-7587	
Nancy Kim,	NYS DOH	518-402-7511	518 402-7509
Lynn Beasley	EPA/Superfund	703 603 9086	703 603 9104
George Alexeeff	OEHHA/Cal-EPA	510-622-3202	510-622 3210
PAUL TOBIN			
GEORGE RUSCH	UNION CARBIDE HONEYWELL	973 455 3672	973 455 4857
MARQUEA D. KING	U.S. EPA/ OPPT	2025643299	2025647406
ERNEST V. FALKE	U.S. EPA/ OPPT	2025647646	2025647406

AFIOH/RSRE
(Air Force Institute for Occupational Health)
2513 Kennedy Circle, Brooks City-Base, TX 78235-5116
AFIOH Front Office: 210-536-2000
RSRE Office: 210-536-6121
RSRE FAX: 210-536-1130
Contact (Mr. John P. Hinz): 210-536-6136

JANUARY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

FEBRUARY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29						

MARCH 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

APRIL 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

MAY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23/30	24/31	25	26	27	28	29

JUNE 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

JULY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

AUGUST 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

SEPTEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

OCTOBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24/31	25	26	27	28	29	30

NOVEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

DECEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

NAC-AEGL #31

(National Advisory Committee for Acute Exposure Guidelines for Hazardous Substances)

San Antonio, TX

December 10-12, 2003

US AIR FORCE

Name	Organization	Phone	FAX
Richard D Thomas	Intercet, Ltd	703-734-1454	-3274
Johan Schefferle	RIVM Netherlands	+31302743660	-4475
Marc Ruijten	RIVM Netherlands	+31 30 2744566	-4088
John Morawetz	ICWA	513-626-8882	-8847
Bob Benson	EPA Region 8	303-312-7070	313-312-6131
George Rodgers	AAFCL	502-852-3782	502-852-4093
Tom Hornshaw	IL EPA	217-785-0832	217-782-1431
Loren Koller	Environmental Health Trust	541 745-5131	541-745-5731
Jonathan Borak	ACOEM/Yale	203-777-6611	203-777-1411
Kawethu Davidson	ORNL	865-574-7799	865-574-5353
Sylvia Milnes	ORNL	865-576-2964	865-574-9858
Susan Ripple	Dow	989-636-5572	9896389975
STEPHEN BJARNASON	DRDC (CANADA)	403-544-4990	403-544-4714
KENNETH L. PAVKOV	ExxonMobil Biomedical	908-730-1067	908-730-1199
Roberta L. Grant	Texas Commission on Environmental Quality	512 239-4115	512 239-1794
Abha Kochhar	" "	(512)239-1075	" "

AFIOH/RSRE
(Air Force Institute for Occupational Health)
2513 Kennedy Circle, Brooks City-Base, TX 78235-5116
AFIOH Front Office: 210-536-2000
RSRE Office: 210-536-6121
RSRE FAX: 210-536-1130
Contact (Mr. John P. Hinz): 210-536-6136

JANUARY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

FEBRUARY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29						

MARCH 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

APRIL 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

MAY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23/30	24/31	25	26	27	28	29

JUNE 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

JULY 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

AUGUST 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

SEPTEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

OCTOBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24/31	25	26	27	28	29	30

NOVEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

DECEMBER 2004

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

ATTACHMENT 4

Public comments on the Proposed Acute Exposure Guideline Levels (AEGLs) for Ammonia

and responses to the comments

by

Kowetha Davidson
Oak Ridge National Laboratory

NAC/AEGL Meeting, San Antonio, TX
December 10-12, 2oo3

Comments from TFI

II. Comments Regarding AEGL-1 Values

The National Advisory Committee (NAC) defined the AEGL-1 as follows:

> AEGL-1 is the airborne concentration (expressed as parts per million (ppm) or milligram/meter cubed (mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. (FR 68 at 42712)

As stated in the text of the proposal, "the AEGL-1 value of 25 ppm is based on the concentration "**slightly below the lowest concentration showing irritation in humans**." The Committee needs to reconcile this statement with the definition above – as this does not correlate with the definition of AEGL-1 representing notable discomfort or irritation. The AEGL-1 levels are apparently being based upon odor threshold concentrations, as evidenced both from docket transcripts as well as personal obervation at the NAC meetings. The AEGL-1 should be based upon thresholds for *notable discomfort* in accordance with the NAC's definitions. In the case of ammonia, airborne concentrations associated with discomfort are greater than odor threshold concentrations.

As summarized in the notice:

> "Experimental studies on human volunteers showed that *slight irritation* occurs at 30 ppm (10 minutes), *moderate irritation* to the eyes, nose, throat, and chest occurs at 50 ppm (30 minutes to 2 hours), *highly intense irritation* occurs at 110 ppm (30 minutes to 2 hours), *unbearable irritation* occurs at 140 ppm (30 minutes to 2 hours), and *excessive lacrimation and irritation* at 500 ppm."

There are no data cited in the proposal that demonstrate any adverse effects at the proposed level of 25 ppm. By definition, the AEGL-1 level is an effect level (airborne concentration *at or above* which the individuals could experience *notable discomfort*). The lack of data showing effects that meet the AEGL-1 definition at 25 ppm would appear to preclude its use as the AEGL-1 value. The available data suggests that the *moderate irritation* observed at 50 ppm is consistent with the AEGL-1 definition.

OSHA sets permissible exposure levels (PELs) to protect workers against the health effects of exposure to hazardous substances. PELs are regulatory limits on the amount or concentration of a substance in the air. PELs are enforceable. [http://www.osha.gov/SLTC/pel/index.html] The current OSHA PEL for ammonia is 50 ppm. If the NAC would contrast this value with the proposed 25 ppm a significant intellectual disconnect arises. OSHA would not allow workers to be regularly exposed to levels that would cause notable discomfort or irritation.

Response: *AEGL-1 was based primarily on odor threshold. These values were proposed and adopted by the NAC/AEGL Committee prior to the publication of the Standing Operating Procedures (SOP). AEGL-1 values are no longer develop based on odor detection. The NAC/AEGL Committee will review these values based on the current SOPs.*

III. Comments Regarding AEGL-2 Values

As with the AEGL-1, the Committee injects an additional (yet unquantified) safety factor into the AEGL-2 development process. The definition for AEGL-2 cites "irreversible or other serious, long-lasting effects or impaired ability to escape." Yet, the recommended AEGL-2 values are based upon the Verberk study (1977), in which the observed effects were nondisabling and reversible. The formal definition of the AEGL-2:

> AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

The statement that 'at least one of eight subjects reported nuisance or offensive irritation to the eyes and throat during exposure to 110 ppm of ammonia for one hour.' So, seven of eight (87.5%) non-expert (and thus susceptible) subjects tolerated 110 ppm and one described it in terms that seem to fit the AEGL-1 definition. The most serious effects observed in the Verberk study occurred following exposures to 140 ppm ammonia for between 30 minutes and 1 hour when four subjects termed their exposure "unbearable" and left the exposure chamber. Clearly, there was no impaired ability to escape under these conditions. Several tests of respiratory function were conducted on the exposure subjects; there was no evidence of adverse effects from these measures. Thus, there were no effects observed in this study that meet the definition for AEGL-2 effects. The new draft document even states that intolerable or unbearable concentrations "are likely to be lower than those causing irreversible damage to the respiratory tract." Again, it is important to note that the AEGL-2 definition is an effect level (airborne concentration at or above which the individuals could experience irreversible or other serious, long-lasting effects or impaired ability to escape). It is therefore inappropriate to use the results of the Verberk study to set AEGL-2 values in this manner. Once again, the committee has chosen to add an additional, unquantified safety factor into the process. There is a perception on TFI's part, based on the text of the notice as well, observation of several meetings, and transcripts of meetings, that the committee feels the need to inject further conservatism into the process. This 'interpretative' aspect of the Committee's function is not stated in the Standard Operating Procedures (SOP) developed by the NAC.

Furthermore, if sufficient and appropriate data on humans do not exist for establishing a true "effects threshold concentration" for disabling effects following ammonia exposure, then, consistent with NRC guidance, the NAC should not propose AEGL-2 values when there is not a sound scientific basis to do so.

Response: *The study by Verberk (1977) is appropriate for deriving aegl-2 values. The responses were subjective as would be the response of the general population in case of an accidental exposure. A range of responses were recorded by the individuals at each concentration and exposure time as would be the case for the general population. In order to consider the sensitive population, the response of the most sensitive individual(s) in the study is taken as the endpoint for deriving AEGL values. If the average response had been used for deriving AEGL-2 values, then application of an uncertainty factor of 3 may have been justified. Therefore, the*

concentration and time associated the greatest response of an individual was used for deriving AEGL-2 values.

TFI would assert that there is no technical basis for the application of the ten Berge equation to non-lethal responses in any species.
The proposed AEGL-2 values in the new draft document are based on the ten Berge equation ($C^n \times t = k$, where $n = 2$ and k is a constant), applied to the results of Verberk for 140 ppm and a 1-hour exposure. The ten Berge equation was developed using only lethality data. The new draft document provides no rationale for the use of ten Berge extrapolations on non-lethal toxicity endpoints. The appropriateness of such extrapolations has not been established.
The failings of the ten Berge extrapolation for non-lethal effects is illustrated by deriving a 2-hour AEGL-2 value using the same procedures employed in the proposed recommendations. The 2-hour AEGL-2 is 100 ppm, a level at which the same effects should be observed as those reported for the 1-hour exposure to 140 ppm. However, Verberk exposed subjects to 110 ppm for 2 hours and did not observe the same "unbearable" irritation reported in the 140 ppm/1-hour exposure group.

Response: *The NAC/AEGL Committee recognized that the AEGL-2 values for the longer term exposures did not follow ten Berge's extrapolation. The value of n=2 implies that the effects of ammonia particularly at the lower concentrations are more a function of concentration than time. In addition, adaptation to low exposure concentrations occurs during longer exposures. The value proposed for the 4- and 8-hour AEGL-2 levels is the same as proposed for a 1-hour exposure and should be protective of serious effects occurring when exposure exceeds a 1-hour duration.*

IV. Comments Regarding AEGL-3 Values

The definition of AEGL-3 as described in the FR notice:

> AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

TFI believes that the human dose-response data from accidents are very relevant to AEGL-3 values and should be considered. While acknowledging that there are uncertainties associated with the accident reconstruction models (e.g., gas dispersion models), this does not entirely negate the usefulness of the human data. Such uncertainties have not precluded the use of these models in other exposure assessment contexts. For example, gas dispersion models are an important component of accidental release analysis that will be required under EPA's RMP rule and are also included in EPA technical guidance documents that describe refined approaches for determining the maximum impact distance in the case of an accident. Yet, the AEGL values promulgated discount all of the human data in determining AEGL-3 values, and cite very limited references overall. Even if the data derived from models of accidental exposures to humans is inadequate to function as the sole basis for deriving AEGL-3 values, these data may play an important and invaluable role as a "biological check" of the AEGL-3 values based on animal data.

For example, the "zero lethality" (LC_{01}) concentration predicted by Pedersen and Selig probit equation for vulnerable individuals is 3,356 ppm for a 1-hour exposure. This value is about three times higher than the proposed AEGL-3 value based on mouse data, but is similar to AEGL-3 values based on rat data. If animal data are to be used in developing AEGL-3 values, they should be based upon the rat data of Appleman et al. (1982). Earlier drafts of the background document concluded that the data generated from the rat studies of Appleman et al. are more appropriate for extrapolating lethal doses in humans, primarily because the data set was more complete in that multiple exposure concentrations and multiple exposure durations were incorporated into the test protocols. The latest notice now asserts that the mouse data are more appropriate for deriving AEGL-3 levels due to the more sensitive lethality response observed in mice compared to rats. There are two areas of concern with this conclusion:

Mice are recognized to be more sensitive to the lethal effects of irritants than other animals, including rats. (ten Berge et al., 1986, whose work is cited extensively in generating AEGL levels. Also Appelman, et al., 1982, and Klaassen, 1996), These references which studied the lethality of several irritants in a range of animal species conclude that the conspicuous sensitivity of mice renders data on lethal doses in mice not appropriate for predicting mortality in humans. The document that supports the Federal Register notice cites increased confidence in the mouse data because of the similarity between two mouse studies in their 1-hour LC_{50} estimates. One problem with this approach is that it ignores the other mouse LC_{50} data reported in the document, data that is not consistent with the former two studies. A second problem is that, unlike the rat data, the mouse studies were conducted at only one exposure duration. Given that the data from the single exposure duration will be extrapolated to several exposure durations in deriving AEGL-3 values, additional uncertainty is incorporated into the derived values from using the single duration mouse data.

Differences in dose delivered to the target tissue in humans versus rats (for a given exposure concentration) should be taken into account (i.e., human equivalent concentrations). In earlier versions of the draft document, the regional gas dose ratio (RGDR) approach outlined by the EPA was used to account for species differences. For example, the increased sensitivity of the mouse to irritants may be a function of its respiratory physiology, ventilation rate, etc. In the new draft document, all references to this approach are gone, with no rationale for why such a correction for interspecies differences, one that is consistent with EPA policy, is no longer relevant.

There is not a sound scientific basis for AEGL-3 values for exposure durations greater than one hour. Consistent with NRC and National Institute for Occupational Safety and Health (NIOSH) guidance, the NAC should not propose AEGL-3 values when there is not a sound scientific basis to do so. At best, the ten Berge equation is applicable to a limited range of exposure durations, concentrations, and species. There is no scientific basis for its application to humans for exposure durations greater than one hour. Although the test in the new draft document is in agreement with the above statement, the tables in the new draft document listing the recommended AEGLs still contain AEGL-3 values for 4- and 8-hour exposures.

Response: *The mouse is indeed more sensitive to inhaled ammonia than the rat. In using the mouse data, the interspecies factor was reduced from 10 to 1 in acknowledgment of the*

increased sensitivity of the mouse. If the rat data had been used to derive AEGL-3 values an interspecies uncertainty factor (UF) of at least 3 along with an intraspecies factor of 3 would have been applied to the LC_{01}, and the AEGL values derived from rat data would have been lower. Based on Appelmam's data and using the regression coefficients to extrapolate to LC_{01} value (and the pertinent time frames and applying a total UF of 10, the AEGL values would be 3400, 2400, 1400, 1000, 500, and 360 ppm for 5, 10, 30, 60, 240, and 480 minutes, respectively, compared with 3800, 2700, 1600, 1100, 550, and 390 ppm, respectively, when derived from the mouse data

Dosimetric adjustment: EPA's dosimetric adjustments were developed for deriving references concentrations for chronic exposure to inhalation toxicants. Because of the uncertainty of applying this methodology to single exposure duration ≤8 hours, it was not applied to AEGL development.

Application of the ammonia AEGL values to duration >1 hour. Although most accidents with ammonia may involve exposure that last for only a short duration, such as the South Africa accident, there are others that may last much longer depending on weather conditions. See the writeup of the railroad accident (Kass et al., 1972), where the fog kept the ammonia close to the ground for a long period of time. This study show that AEGL values for durations >1 hour are needed for emergency planning.

1. V. Potential for Incorrect Interpretation and Regulatory Misuse of AEGLs

Members of the NAC have considerble expertise in the AEGL development process, and well understand the meaning of an AEGL at different levels. This same fact is not likely true with the public, stakeholders, or state regulators who might incorrectly interpret the purpose and intent of AEGLs. A recent example of this is the failed rulemaking in Iowa regarding issuance of ambient air standards for ammonia. Regulators there used minimum risk levels (MRLs) from ATSDR and occupational health limits to justify a proposed ambient air standard of 150 ppb. To

illustrate, page 122 of the Iowa Concentrated Animal Feeding Study (CAFO) report states, "standards for community exposures to the toxic agents released from CAFOs must be stricter than that for occupational exposures..." (Iowa State University, et al., 2002).

Indeed, the misuse of MRLs occurred in Iowa despite ATSDR's warning:

> MRLs are estimates intended for use as screening levels by ATSDR health assessors to identify contaminants and potential health effects of concern at hazardous waste sites. The ATSDR disclaimer states, "It is important to note that MRLs are not intended to define clean-up or action levels for ATSDR or other Agencies." It is overtly restrictive to utilize such levels as ambient air quality standards. Indeed, ATSDR states, "Exposure to levels above the MRL does not mean that adverse health effects will occur... the resulting

MRL may be as much as a hundredfold below levels shown to be nontoxic in laboratory animals."

As is evident from the Iowa example, the potential for misuse of AEGLs is great even among those in the academic and regulatory community. It is imperative that the NAC communicate the intended uses of AEGLs and perhaps more importantly what they are not intended for. The AEGL-1 of 25 ppm is likely the value with the highest potential for incorrect interpretation.

VI. Conclusion

In its previous comments, TFI has discussed the inconsistent use of uncertainty factors in extrapolating animal data to humans and expressed concern over unnecessary conservatism in the use of such factors. It is therefore important to note that the NAC has appeared to develop a more uniform and appropriate approach towards the use of uncertainty factors, and should be commended for doing so.
We hope that the members of the NAC will take these comments into their deliberations and revise the final AEGLs. TFI believes that the implementation of these comments will result in the best scientifically justifiable AEGL values. In addition, TFI would like to see that the references contained in the bibliography, if not already incorporated into the formal EPA docket and review process for this issue; be reviewed and incorporated into the decision-making process for final AEGLs.

Response: The checked (✓) references are already cited in the document. The starred (**) references have been ordered. TFI should provide information on the significance of the remaining references.

TFI appreciates the opportunity to comment on this important rulemaking. Please do not hesitate to contact me at (202) 515-2706 if you have any questions regarding these comments.

Very truly yours,

William C. Herz
Director of Scientific Programs, The Fertilizer Institute

Bibliography

**AIHA [1971]. Anhydrous ammonia. In: Hygienic guide series. Am Ind Hyg Assoc J 32:139-142.

Alarie Y [1981]. Dose-response analysis in animal studies: prediction of human responses. TFI Health Perspect 42:9-13.

✓Appelman LM, ten Barge WF, Reuzel PGJ [1982]. Acute inhalation toxicity study of ammonia in rats with variable exposure periods. Am Ind Hyg Assoc J 43:662-665.

Back KC, Thomas AA, MacEwen JD [1972]. Reclassification of materials listed as transportation health hazards. Wright-Patterson Air Force Base, OH: 6570th Aerospace Medical Research Laboratory, Report No. TSA-20-72-3, pp. A-172 to A-173.

✓Boyd EM, MacLachlan ML, Perry WF [1944]. Experimental ammonia gas poisoning in rabbits and cats. J Ind Hyg Toxicol 26:29-34.

Deichmann WB, Gerarde HW [1969]. Trifluoroacetic acid (3FA). In: Toxicology of drugs and chemicals. New York, NY: Academic Press, Inc., p. 607.

Flury F [1928]. Moderne gewerbliche vergiftungen in pharmakologisch-toxikologischer hinsicht (Pharmacological-toxicological aspects of intoxicants in modern industry). Arch Exp Pathol Pharmakol 138:65-82 (translated).

✓Henderson Y, Haggard HW [1943]. Noxious gases. 2nd ed. New York, NY: Reinhold Publishing Corporation, p. 126.

Iowa Concentrated Animal Feeding Operations Air Quality Study. Final Report. Iowa State University And The University Of Iowa Study Group, February 2002.

Klaassen, CD. [1996]. Toxicology: The Basic Science of Poisons. Fifth Edition. McGraw Hill Publishers, NY, NY.

✓Kapeghian JC, Jones AB, Mincer HH, Verlangieri AJ, Waters IW [1982]. The toxicity of ammonia gas in the mouse. Fed Proc 41:1568 [Abstract #7586].

✓Mulder JS, Van der Zahm HO [1967]. Fatal case of ammonium poisoning. Tydschrift Voor Sociale Geneeskunde (Amsterdam) 45:458-460 (translated).

**NRC [1987]. Emergency and continuous exposure guidance levels for selected airborne contaminants. Vol. 7. Ammonia, hydrogen chloride, lithium bromide, and toluene. Washington, DC: National Academy Press, Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council, pp. 7-15.

✓Silverman L, Whittenberger JL, Muller J [1946~~4~~9]. Physiological response of man to ammonia in low concentrations. J Ind Hyg Toxicol 31:74-78.

Smyth HF Jr [1956]. Improved communication: hygienic standards for daily inhalation. Am Ind Hyg Assoc Q 17(2):129-185.

Tab Biol Per [1933]; 3:231-296 (in German).

✓ten Berge WF, Zwart A, Appelman LM [1986]. Concentration-time mortality response relationship of irritant and systematically acting vapours and gases. J Haz Mat 13:301-309.

U.S. Bureau of Ships [1962]. Submarine atmosphere habitability data book. AVSHIPS 250-649-1. Rev. 1. Washington, DC: U.S. Department of the Navy, U.S. Bureau of Ships, p. 629.

Comments from Mary Lee Hultin

DRAFT
OPPT Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPT)
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Dear OPPT Document Control Office:

SUBJECT: Comments re: docket ID number OPPT-2002-0027 Federal Register, Vol. 68, No. 138/Friday, July 18, 2003/Notices

The following comments are being offered pursuant to the Federal Register Notice issued July 18, 2003, regarding Proposed Acute Exposure Guidance Levels (AEGL):

Comments on Ammonia

For each of the three AEGL levels, a baseline exposure concentration was established to calculate concentrations for different exposure durations. These baseline concentrations seemed appropriately selected based on the scientific literature. But the final concentration established from applying uncertainty factors (UF) was troubling. This reviewer does not concur with the AEGL Committee justification for the use of an UF of 1. Using an UF of 1 means that there is 100% certainty that the proposed exposure concentrations will not effect sensitive subpopulations. This reviewer questions whether 100% certainty can be assumed in this case. Uncertainty factors are designed to lower exposure concentrations when there are study gaps, incomplete, anecdotal, or surrogate data.

[**Response:** *We do not try for 100% certainty, because it cannot be attained under any circumstances even by using additional uncertainty factors. For ammonia, the AEGL values were based on exposures to healthy volunteers, workers, or military personnel.*

Far different outcomes might have resulted if testing had been conducted on children, the elderly or people with respiratory sensitivities.

[**Response:** *College students, not military personnel nor workers were involved in the study that served as the basis for AEGL-2. This type of testing would not be done on children.*]

The AEGL committee stated that they accounted for the sensitive subpopulations by the use of an UF 1. Using a UF 1 does not adjust the exposure concentration to account for sensitive individuals. The rationale that ammonia is efficiently scrubbed from the nasal passages, thereby eliminating the chance that an asthmatic would react is describing an unproven protective process for a respiratory condition that is not completely understood. The complete etiology of asthma is unknown. This reviewer is not aware of clinical studies that show a statistically significant

sample of asthmatics or surrogate laboratory animals do not react to airborne concentrations of ammonia. If there aren't any clinical studies to show this, the uncertainty factor is necessary to account for lack of exposure data for cause/effect and an incomplete understanding of this medical condition.

Response: *An uncertainty factor of 1 was applied for several reasons. The most sensitive response of the most sensitive individual at 110 ppm was used instead of the average response for the group; the response was subjective, i.e. the perception of irritation was not accompanied by physical evidence of irritation. For example, eye irritation was perceived, but no redness or lacrimation was reported; chest irritation was perceived, but no effect of respiratory function was found among any of these subjects.: In one study reported by McLean (1979), atopic subjects, which included asthmatics, did not response significantly different from non-atopic subjects to ammonia introduced into the nostrils at concentrations up to 100 ppm.*

Another reason the committee gave for a reduced uncertainty factor was that children don't seem to be as sensitive to ammonia as adults. One example used was that children have quicker response time of reflex glottis closure than older individuals. This condition seems to be age dependent. Perhaps the elderly would therefore be a sensitive subpopulation. Another example was a mother carrying her child through an accidental ammonia release. The child apparently suffered no adverse effects, while the mother did. Besides the child's apparent tolerance for ammonia (maybe from glottis closure, maybe not), another reason could be that the mother shielded the child, thereby lessening exposure. Parents typically shield their children from harm rather than shield themselves; e.g., putting a coat across a child's face, or pressing the child's face against their body. Since it could not be determined from the background document how the mother carried the child, uncertainty exists.

Response: *Regardless of whether the mother put something over the baby's face, the only air available for breathing for 90 minutes contained high levels of ammonia. The mother was unconscious part of the time thus rendering her incapable of shielding her child. The child suffered a chemical burn on its body indicating that exposure was intense.*

It seems plausible to account for this uncertainty with an UF of greater than 1. It is strongly urged that the AEGL Committee re-evaluate their use of uncertainty factors since the data used to establish the AEGL values is not 100% certain. It is also strongly urged that they re-examine the statement in the Federal Register Notice (FR68, No. 138, p.42712) under Background - Characterization of the AEGLs: "it is believed that these recommended exposure levels are applicable to the general population including infants and children, and other individuals, who may be sensitive and susceptible."

[**Response:** *The AEGL derivations do take into account the sensitive members of the population; however, hyperpsensitive members of the population may respond adversely to the ammonia concentrations proposed in this document. An attempt was made to make use of all information available on ammonia. The available data show that children may not be as sensitive as adults to inhaled ammonia; atopic subjects did not respond differently from non-atopic subjects. The*

database for children and asthmatics is generally very small, but we use whatever data are available.

If you have questions regarding this correspondence, please contact me.

Sincerely,

Mary Lee Hultin
Toxicology Specialist
Air Quality Division
MDEQ

Comments from George Alexeeff

August 17, 2003

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPTS)
Environmental Protection Agency
1200 Pennsylvania Avenue
Washington, DC 20460-0001

Docket Control # OPPTS-2002-0027: Ammonia AEGL-2 and 3 Values

I would like to raise concerns regarding the AEGL-2 and 3 values recommended by the AEGL Committee for Ammonia.

The AEGL-2 is based on human data indicating that unbearable irritation occurs at 140 ppm between 30 to 120 minutes of exposure, depending on the "non-expert" individual. This is generally described in the text and Executive Summary. However, there are numerous locations throughout the text and tables that incorrectly describe this information. I suggest the following changes be made to improve the clarity and consistency of the AEGL-2 derivation.

- The Endpoint described in the Summary Table (page viii, line 6), that is "irritation: eyes and throat; urge to cough" is incorrect. It should be revised to "NOAEL for unbearable irritation (Verberk, 1977)," to be consistent with the document.

Response: *To use the term "NOAEL for unbearable irritation" is ambiguous because effects were observed below the concentration that were associated with unbearable irritation. Therefore, this concentration is not a no-adverse-effect level (NOAEL). Further, NOAEL implies that no effect was observed at the concentration used to develop the AEGL-2 values, and NOAEL is not descriptive of the response at the concentration that served as the basis for AEGL-2 derivation. NOAEL was first used for RfD/RfC derivation for chronic exposures. It would be confusing to our audience to use terminology that has different meanings depending on the circumstances.*

On page vii, line 2, of the Executive summary should be added "the remaining subjects reported the effects to be unbearable before the two-hour exposure period ended."

Response: *Modify to read "At the next highest concentration, some of the subjects reported the effects to be unbearable and left the chamber between 30 minutes and 1 hour; none remained for the full 2 hours."*

- The justification for the uncertainty factor of 1 on page vii, states: "An intraspecies uncertainty factor of 1 was used for deriving the AEGL 2 values because the responses of the non-expert group ranged from just perceptible to offensive, but the AEGL-2 value was based on the response of the most sensitive individuals." This is incorrect. It should be replaced with: "An intraspecies uncertainty factor of 1 was used for deriving the AEGL 2 values because the responses of the non-expert group are assumed to reflect

responses similar to sensitive members of the population, based on familiarity with chemical exposures. This is evident by the lack of similar responses from the 'expert' group." A similar revision needs to be made on page 31, line 2.

Response: *There were a range of responses for members in the non-expert group, but the only response that justified using the 110-ppm concentration for AEGL-2 derivation was the offensive response; otherwise, the responses would have been too mild to use for AEGL-2 derivation. Therefore, the AEGL-2 derivation was based on the response of the most sensitive individual(s) in the non-expert group. Change sentence to read: An intraspecies uncertainty factor of 1 was used for deriving the AEGL-2 values because the responses of the non-expert group ranged from "just perceptible" to "offensive". The AEGL-2 values were based only on the response ("offensive") of the most sensitive individual(s) in the group.*

- The effects described in the Table 9 (page 30, lines 5 and 6), that is "irritation: eyes and throat; urge to cough" is incorrect. It should be revised to "NOAEL for unbearable irritation (Verberk, 1977)," to be consistent with the document.

Response: *Same as above*

- The AEGL derivation (page 30, line 29) should be revised to state that: "Based on the no observed adverse effect level of 110 ppm for the unbearable irritation which occurred at 140 ppm, following 30 minutes to 2 hours of exposure in the non-expert subjects (Verberk, 1977), the proposed AEGL-2 level for 1 hour is 110 ppm."

Response: *The 110-ppm concentration is not a NOAEL, which is the concentration at which* ***no*** *adverse effects are observed. There are instances when AEGL values are based on concentrations and durations at which no effects (adverse or otherwise) are reported; therefore, the terms NOAEL or NOEL should not be used in a confusing or ambiguous manner. For example, the AEGL-2 for ethylenimine was an actual NOEL for extreme respiratory difficulty, because no effects were observed at that concentration, and no other data were available for AEGL derivation.*

- To be consistent with the document the Endpoint/Concentration/Rationale on page 56 should be revised to: "For the non-expert exposure group, 110 ppm for 1 hour produced highly intense odor; highly intense eye, nose, throat, and chest irritation, moderate urge to cough, and moderate general discomfort. The range of responses at 2 hours was very similar to that at one hour. The non-experts considered the effects to be near the maximum response (offensive), whereas the expert responses were always of a lesser degree. This was determined to be the NOAEL for unbearable irritation."

Response: *The description as written in the document is representative of the study. Same comment as above for NOAEL.*

- Appendix C derivation, page 51, line 5, the toxicity endpoint should be revised to: "NOAEL for unbearable irritation (Verberk, 1977)," to be consistent with the document.

The AEGL-2 values for 1, 4 and 8 hours are appropriately set at the no effect level of 110 ppm from Verberk for the symptoms reported. However, the 30-minute value appears to require revision for consistency. The AEGL 2 value for 30 minutes should also be set at 110 ppm. At 30 minutes the range of responses at 30 minutes (Verberk 1977); included unbearable eye irritation as indicated in Figure 2, unbearable throat irritation as indicated in Figure 3; and unbearable cough as indicated in Figure 4.

Currently the shorter time points are estimated using: "$c^n \times t = k$; where c is concentration, t is exposure time and n is 2 (ten Berge et al., 1986). This is one option for adjusting to 5 and 10 minutes. If the 30-minute AEGL-2 is revised to 110 ppm the 5 and 10 minute values would have to be revised to 270 and 190 ppm, respectively. However, it may be more justifiable to retain the 110 ppm value at all exposure times, especially since no uncertainty factors were used in the calculations.

Response: *Another study showed that human can breath concentrations of ammonia up to 500 ppm for 30 minutes without serious effects. It is valid to use the ten Berge equation for ammonia, where n = 2. 110 ppm for 10 minutes is extremely unreasonable for 5- and 10-minute values considering the exposures at Potchefstroom, South Africa. The South Africa accident resulted in a large amount of ammonia being released into the air. Because of the extremely large amount released, it is reasonable to assume that the concentrations were very much in excess of 110 ppm; nevertheless, the people had the ability to escape the fumes. Although the students described their responses as offensive or unbearable, no residual effects (sores in the nose or redness of the eyes or throat) were described by the author and none of the exposures had an effect on respiratory function.*

The use of the interspecies factor of 1 for deriving AEGL 3 should be further justified. The document states that: "The mouse is the most sensitive species to exposure to respiratory irritants, including ammonia. Because of the higher sensitivity of the mouse, an interspecies uncertainty factor of 1 was applied to the mouse data." This argument is insufficient since the interspecies factor is to evaluate the sensitivity between mice and humans, not between mice and another animal species such as rats. Furthermore it would be helpful if the specific study or part of the document was referenced so that the comparison could be verified.

Response: *ten Berge et al. (1986) noted the unusual sensitivity of the mouse to respiratory irritants. We have used comparisons between species to justify the interspecies uncertainty factor. Will insert reference to ten Berge.*

The derivation of AEGL-3 goes on to say: "An uncertainty factor of 3 for interspecies sensitivity combined with an intraspecies uncertainty factor of 3 (total uncertainty =10) would result in an 30-minute AEGL-3 value comparable to the 500 ppm shown to be tolerated by humans without lethal or long-term consequences (Silverman et al., 1949)." While this may be technically true, the comparison in not necessarily justified. The Silverman et al., (1949) study was not composed of members of the sensitive subpopulation of concern. Instead, the subjects of the Silverman et al., (1949) study were sedentary and were exposed oral/nasally only. The AEGL-3 was correctly derived from a concentration that did not produce lethality in mice. It is unclear why the document created an expectation that the AEGL-3 value for humans should be producing lethality. If the AEGL-3 values were known to produce little toxicity, it could see the justification for eliminating the uncertainty factor completely, but it is not clear why a factor of 2 was not used if 3 produced concentrations that conflicted with existing human data.

Response: *There is no basis for using an uncertainty factor of 2. Uncertainty factors should not be arbitrarily manipulated in order to lower AEGL values. Further, the effects associated with the exposure to 500 ppm for 30 minutes are not even at the AEGL-2 level. After reviewing the derivation section (AEGL-3), no reference was made to an expectation of lethality at the AEGL-3 concentrations*

I request that the Committee consider these recommendations and revise the AEGL documents accordingly.

General Response: *Ammonia was discussed by the NAC/AEGL Committee approximately six times. Consensus was reached on all three AEGL levels. It is past time for the NAC to bring closure to its discussion of this chemical on issues raised by committee members.*

Sincerely,

George V. Alexeeff, Ph.D., D.A.B.T.

Comments from John Morawetz

August 15, 2003

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460-0001

Docket control # OPPTS-2002-0027: Ammonia AEGL-2 and 3 values

I would like to raise concerns regarding the AEGL-2 and 3 values recommended by the AEGL Committee for Ammonia.

Verberk's subjects symptoms and time when leaving the chamber

The endpoint used for AEGL-2 should be the no effect level for "unbearable" symptoms and the inability for non expert subjects to remain in the exposure chamber (Verberk, 1977). This would change the text in the Executive Summary Table ("irritation: eyes and throat; urge to cough"), AEGL derivation, Appendix B ("irritation: eyes and upper respiratory tract") and Appendix C derivation ("offensive"). This does not change the AEGL-2 values for 1, 4 and 8 hours which are appropriately set at the no effect level of 110 ppm from Verberk for these symptoms but would change the 5, 10 and 30 minute values.

Response: *A "no-effect-level for unbearable symptoms" is not meaningful, because it could mean that no effects whatsoever were noted. This is not the case. It is best to use a description of the endpoint used to derive the AEGL. "No-effect-level" should not be used when effects are observed; its ambiguous. The non-expert subjects were not "unable" to remain in the chamber; they chose not to remain in the chamber. They suffered no physical or functional damage to the respiratory tract. Inability to remain in the chamber is not a response. In human subject research, the subject can terminate any part of the research at any time with no questions asked. The AEGL values for 5-30 minutes are appropriately derived using ten Berge's equation. This was discussed and settled in the NAC meetings.*

In Verberk before leaving the chamber all 8 non expert subjects "scored 5 = "unbearable" for at least one symptom". They all "felt such a severe irritation that they all left the exposure chamber prematurely." Two subjects left the chamber at 4 time periods (30, 45, 60 and 75 minutes) but this did not take place at the next lowest exposure, 110 ppm, for the 2 hour study. The effect of "unbearable" eye and throat irritation, coughing and general discomfort must be noted in Table 9 as it is in Table 4. This should also include the leaving of the exposure chamber prematurely by all non expert subjects from 30 to 75 minutes which is not in either Table 4 or 9. On the significance of using non expert subjects the author states: "in the situation of a sudden, unexpected exposure, the subjective responses of an ignorant public will be more alike those of the non-expert group than those of the experts" exactly the population the AEGL committee is mandated to protect.

Response: *The responses of the subjects were subjective. There was no physical evidence of irritation to the respiratory tract or eyes in these subjects. Leaving the chamber is not an effect. Human subjects may terminate any part of their involvement in a study at any time during the study.*

These subjects exercised their prerogative to do so. The response of the subjects was "urge to cough" not coughing. There is a difference.

The AEGL 2 value for 30 minutes should therefore be set at 110 ppm since 2 of 8 non expert subjects classified a 140 ppm exposure as unbearable at 30 minutes and left the chamber. All 8 non experts remained in the chamber for 2 hours at 110 ppm. There are some serious considerations to extrapolating to the 5 and 10 minute time periods with no uncertainty factors and an n of 2. These include that all 8 non expert subjects left the chamber at 140 ppm within 75 minutes, they were all young students (age 18-30), there were a relatively small number of subjects (8) and there was a range in chamber exiting time from 30 to 75 minutes. I propose that either an intraspecies uncertainty factor of 2 be used for extrapolation to 5 and 10 minutes to account for these limitations or an n of 3 be used for extrapolation to the shorter time periods. These values are supported by the ability of all the Industrial Bio-Test Labs subjects to remain in the chamber for 5 minutes at 143 ppm. Verberk supports this position: "even when a PEL is based upon the effects of the non-expert group, it is desirable to introduce a safety factor in order to protect the more vulnerable individuals in the general population".

Response: *The subjects left the chamber after 30 minutes not at 30 minutes. If I stated that in the document it was in error. The value of n was derived empirically; it should not be arbitrarily changed just to get lower values; nor should uncertainty values be manipulated just to push AEGL values lower.*

AEGL-3 Interspecies Uncertainty Factor of 1

The use of the interspecies factor of 1 for deriving AEGL 3 is a decision that should be backed up by a significant amount of data. With only a proposed intraspecies factor of 3 the current recommendations will be one third the LC01 mouse values.

First, the ammonia document summarizes lethality data in three species, rats, mice and cats (Tables 5, 6 and 7). The cat lethality data suggests that mice may not be the most sensitive species, or that some additional AEGL-3 reduction should occur at the 10 minute level. If the cat data are discarded because of their quality or because there was only one death in 20 animals, then we can only draw conclusions regarding lethality from 2 species.

Response: *ten Berge et al. (1986) noted that the mouse is unusually sensitive to irritants. No such claim has been made regarding humans. The unusual sensitivity of mice to respiratory irritants has been discussed in the NAC/AEGL meetings.*

Second if the AEGL committee is going to use the mouse as the most sensitive species and therefore expects essentially identical human response, we should have fairly stable mouse data but there is variability in data from the primary mice studies. Table 7 lists mouse data that resulted in the same mortality (25-30%) with some inconsistencies that would not be that serious as long as an interspecies uncertainty factor is used. Kapeghian, 1985 had the same mortality at essentially the same concentration (4,380 ppm) as MacEwen, 1972 (4,550 ppm) but at 4 times the time period (240 vs. 60 minutes). Silver, 1948 found 25% mortality at 10 minutes at an exposure that is approximately one third of the proposed AEGL-3 values (8,723 vs. 2,700 ppm). Hilado, 1977 had the same mortality at 30 minutes as Kapeghian, 1982 at 60 minutes but at almost 5 times the exposure level. In addition, the exposures of the two key studies had somewhat different results

which again are cause for concern if an interspecies uncertainty factor of 1 is used. MacEwen, 1972 had 3 of 10 mice die at 4,550 ppm while Kapeghian, 1982 had 8 of 12 die at 4,490 (both one hour studies). Although this is limited data, the confidence to use an uncertainty factor of 1 is not strong.

Response: *The 60- minute LC_{50} values for the mouse studies reported by Silver and McGrath (1948), MacEwen and Vernot (1972), and Kapeghian et al. (1982) were similar (4121, 4837, and 4230 ppm, respectively). The 10-minute LC_{50} for the Silver and McGrath study was extrapolated to 60 minutes using n=2. Only one study was out of range; the LC_{50} for the Hilado et al. (1978) was 10,597 ppm; the exposure concentrations were not measured analytically but were calculated. Therefore, the mouse studies showed remarkable consistency. The strongest confidence of using an uncertainty factor of 1 is that a 3 would lower the AEGL-3 value for 30 minutes to an AEGL-2 level.*

Third, there is very limited human evidence for time periods greater than 30 minutes at significant exposures, a rationale used in the current AEGL-3 derivation Section. Silverman's exposures at 1,000 ppm had no time period mentioned in its citation from the 1949 study and reported coughing immediately. Erskine's exposure to 1,790 ppm was from a single breath. The main human evidence of non lethal exposures is therefore Silverman's 500 ppm mouth/nose only exposure for 30 minutes to 6 subjects that was unbearable. This is limited evidence that 500 ppm will not be life threatening to the general population and does not contradict setting a 30 minute value at some point between 500 ppm and 1,600 ppm for 30 minutes.

Response: *The writeup of the Silverman study did not use the term "unbearable." The subjects switched to mouth breathing but continued the exposure. We have no measurements of concentrations for the Houston or South Africa ammonia accident. Judging from the amount of ammonia released, the concentrations were very high, yet people survived both accidents.*

In general there should be a stronger database or rationale for an interspecies uncertainty factor of 1. I propose that a modifying factor of 2 be used for all time periods due to the reasons listed above.

Response: *Modifying factors should not be applied arbitrarily just to lower AEGL values.*

I request that the Committee reconsider and lower the specific AEGL-2 and all AEGL-3 levels.

General Response: *Ammonia was discussed by the NAC/AEGL Committee approximately six times. Consensus was reached on all three AEGL levels. It is past time for the NAC to bring closure to its discussion of this chemical on issues raised by committee members.*

Sincerely,

John S. Morawetz

c: Larry Gregoire
Secretary Treasurer's Office
Eric Bray

Michael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Paul Tobin, EPA

DRAFT PROPOSAL FOR AEGL-1 FOR AMMONIA

5 Min.	10 Min.	30 Min.	1 Hour	4 Hours	8 Hours
50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3	50 ppm 35 mg/m^3

Rationale

50 ppm:

- Nasal dryness was reported by 2/10 subjects exposed for 5 minutes (Industrial Bio-Test Lab., 1973).
- Moderate irritation (grade 2) was reported by 4/6 subjects, faint or just perceptible irritation by 1/6, and irritation was not detectable by 1/6 exposed for 10 minutes (MacEwen et al., 1970).
- The greatest response to a 2-hour exposure was nuisance irritation and general discomfort was perceptible (Verberk, 1977).

Rationale

30-32 ppm:

Faint irritation was reported by 2/6 subjects, not detectable by 3/6, and no response by 1/6 (MacEwen et al., 1970).

- Nasal dryness was reported by 1/10 subjects (Industrial Bio-Test Lab., 1973).

Intraspecies Uncertainty Factor and Rationale: UF = 1

Atopic subjects did not respond differently from non-atopic to a brief nasal exposure to 100 ppm.

- A child recovered completely from exposure to ammonia concentrations that left the mother with permanent lung damage.

GEORGE V. ALEXEEFF, PH.D., D.A.B.T.
OEHHA, CAL/EPA

Comments:

AEGL-1

I suggest that the derivation of the AEGL-1 values be revised to improve clarity and understanding. The AEGL-1 derivation (page 38, line 29) states: "The AEGL-1 is based upon slight eye irritation noted in the Hastings et al. (1986) study during a 30-minute exposure to 400 ppm mixed xylenes." The derivation does not state if this is the NOAEL or the LOAEL for the AEGL-1. Later in the paragraph it states that "an intraspecies uncertainty factor of 3 was applied because the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)." This statement suggests the starting point is the NOAEL. The document should be revised to indicate that the starting point, a 30-minute exposure to 400 ppm mixed xylenes, is the NOAEL for the AEGL-1 level. The document should further indicate that at and below the AEGL-1 slight eye irritation may occur since the AEGL-1 does not protect against this effect. Furthermore, the document should identify the LOAEL for AEGL-1. Finally, the derivation requires a different justification for the uncertainty factor of 3 since choosing the NOAEL is the standing operating procedure and not a justification for a specific uncertainty factor. The summary tables should also be revised to indicate that the endpoint is the "NOAEL for notable comfort (or the specific effect)."

AEGL-2

The AEGL-2 is "based upon poor coordination resulting when rats were exposed to 1300 ppm mixed xylenes for 4 hours (Carpenter et al., 1975)." Thus the document is suggesting that the poor coordination is a NOAEL for AEGL-2 effects and consequently poor coordination is an AEGL-1 effect. If this is the case the document should clearly indicate that exposure to 1300 ppm mixed xylenes for 4 hours is a NOAEL for AEGL-2 effects as described in the standard operating procedures. The summary tables should also indicate that it is a NOAEL for AEGL-2 effects. Furthermore the document needs to identify the AEGL-2 effect of concern, that is, the LOAEL for AEGL-2.

In the derivation section for AEGL-2 (page 40, line 5), the document indicates: "An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans." No justification is provided for this statement. Interspecies uncertainty is operationally divided into two factors, tissue dose (toxicokinetics) and tissue response (pharmacodynamics). Each of these factors is understood to contribute an uncertainty of approximately 3-fold. The document makes a toxicokinetic statement that rats receive a greater dose of xylenes than humans; this statement requires additional justification in document. However, there is no discussion regarding the responsiveness of rat tissue to effects of xylenes in comparison to humans. In fact the limited data available suggest that humans may be more sensitive. Carpenter (1975) reported that exposure to 690 ppm for 15 minutes produced dizziness in 4 of 6 individuals. This appears to be an AEGL-2 effect that occurs at a concentration at least

2-fold below that of rats. Consequently, the use of an interspecies uncertainty factor does not appear to be supported by the available data.

On page 4, (line 20), the document explains why the Carpenter (1975) data were not used for the derivation of the AEGL-2 by stating: "If one were to use the highest exposure concentration ... and apply the intraspecies uncertainty factor of 3, one obtains a value of 230 ppm. This concentration is supposed to represent a concentration at which exposed individuals could experience irreversible or other serious, long-lasting adverse health effects, or have an impaired ability to escape." This statement suggests that the AEGL-2 effect would be expected to be present at 230 ppm, the calculated AEGL-2. However, the AEGL-2 definition on page i states it is the concentration "above which it is predicted" that the effect would occur. Consequently, the effect would be expected to occur above 230 ppm, not *at* 230 ppm. If the document had identified the AEGL-2 LOAEL, then the effect would be expected at the LOAEL. Thus, further discussion regarding the use of the Carpenter (1975) study as the starting point for the AEGL-2 appears warranted.

AEGL-3

Greater clarity would be helpful in the tables and derivation of the AEGL-3. In the summary table on page vii, the endpoint for AEGL-3 provided is "rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery." The relevant effect of the experiment is that this the highest non-lethal dose. I suggest that the following be added: "This exposure constituted the NOAEL for lethality in rats." Further, I request that this clarification be added to all similar tables and text in the document and appendices.

The justification for an interspecies uncertainty factor of 1 appears to be insufficient. The justification states: "An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans." As discussed above, the justification may address toxicokinetics, however, it does not address the responsiveness of rat tissue to effects of xylenes in comparison to humans. Additional justification of this uncertainty factor appears warranted.

Response: The suggested changes have been made in the Executive Summary, the Table of AEGL values, and sections 5.3, 6.3, and 7.3.

INTERNATIONAL UNION, UAW

Comments:

Investigation of AEGL-1 Health Effects of Xylene
The U.S. Environmental Protection Agency (EPA) states that AEGL-1 values are airborne concentrations above which members of the general public could experience notable discomfort, irritation or other reversible non-disabling health effects. Studies used as evidence for setting AEGL-1 values should clearly state the methods used to determine whether or not there were health effects. The study by Ogata (1970) looked only at excretion of by-products after controlled xylene exposure, not health effects. It cannot be assumed that there were no health effects at the exposure levels reported in the study because the authors did not look for any health effects. AEGL documents are likely to be used by emergency personnel without access to the original studies. For this reason, the description of human studies and their use as evidence should be as scientifically accurate as possible.

Response: The Ogata et al. (1970) study indeed looked at excretion of metabolites in humans after controlled xylene exposure. However, they also assessed systolic and diastolic blood pressure, pulse rate, flicker value, and reaction time in all volunteers at the beginning and the end of exposures. No effects were observed in these health endpoints.

AEGL-2 Derivation
AEGL-2 values are airborne concentrations above which members of the general public could experience impaired ability to escape, irreversible health effects, or other serious long-lasting health effects. In the reference to multiple human studies at the end of Section 6.3 – AEGL-2 Derivation, it would be better to state that either "no disabling effects" were found or only "mild effects were observed," rather than stating that these studies found "no adverse effects". If this statement were changed, it would be appropriate to use the Ogata study to support the AEGL-2 values.

Response
The sentence:

> **"However, a number of studies demonstrate that this concentration has no adverse effects upon exposed individuals: no adverse effects were observed following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993)."**

will be changed to

> **"However, a number of studies demonstrate that only minor sensory irritation is observed following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993)."**

Ogata et al. (1970) shows no effect on the ability to escape at 200 ppm for 3 or 7 hours and thus supports the AEGL-2 value. However, it is not appropriate to use this study to derive the AEGL-2 value as 200 ppm is far below the threshold for effects on the central nervous system.

AEGL-2 10 minute value

The AEGL Committee for Xylene proposes to set a 10-minute AEGL-2 xylene exposure value of 990 parts per million (ppm). In the Carpenter (1975) study, the highest exposure was 690 ppm for 15 minutes. At that concentration, 4 of the 6 volunteers reported slight dizziness. One of those experienced a slight loss of balance. The severity of these health effects is less than that specified by the AEGL-2 definition. Unfortunately, there are no studies that examined health effects at higher exposures. For this reason, it would be imprudent to set the AEGL-2 value above the 690 ppm level, at which mild health effects have been demonstrated.

Response: The effects noted in Carpenter (1975) would not impair escape. It is therefore appropriate to set an AEGL-2 value above this exposure concentration.

*In setting the 10 minute AEGL-2 value, the committee used blood data * from three studies of resting subjects. Two of these studies however, show that blood Xylene concentrations after exercise are two to three times higher **. Exercising subjects may be more similar to people experiencing a chemical emergency than resting ones. Blood xylene concentrations from exercising subjects rather than resting ones are more appropriate for setting the value.*

Response: As noted in Appendix B, an assumption was made that the inhalation volume and frequency were constant across individuals. To provide sufficient protectiveness for persons experiencing a chemical emergency, a value two standard deviations below the mean was used as the starting point to derive the AEGL-2 and AEGL-3 values for 10 and 30 minutes. In addition, an uncertainty factor of 3 was applied for intraspecies variability.

AEGL-3 10 minute value

The AEGL-3 value is the airborne concentration of a substance above which it is predicted that members of the general public could experience life threatening health effects or death. To set this value, the committee used blood data from the same studies used to set the AEGL-2 10 minute value. Again, blood xylene concentrations from exercising subjects rather than resting ones are more appropriate for setting the value. In order to account for varying degrees of vulnerability among different people in setting the AEGL-3 values for exposures lasting 1-8 hours, the committee divides by three so that exposure below the AEGL value will not do serious harm to someone who is three times more vulnerable than most people. However, in setting AEGL-3 values below one hour, the committee reduces the value only by 18%. This does not provide an adequate margin of safety.

Response: As noted in Appendix B, an assumption was made that the inhalation volume and frequency were constant across individuals. To provide sufficient protectiveness for persons experiencing a chemical emergency, a value two standard

deviations below the mean was used as the starting point to derive the AEGL-2 and AEGL-3 values for 10 and 30 minutes. In addition, an uncertainty factor of 3 was applied for intraspecies variability.

* See Table 11, p.37 of Proposed Acute Exposure Guideline Levels for Xylene

** Laine (1993) found that, at 200 ppm, there was more than a two fold increase after 10 minutes of exercise (17 vs. 43 μmol/l). Hake (1981) found that, at 150 ppm, there was almost a 3-fold increase after 11 minutes of exercise (4.6 to 12.5 ppm;). In addition Gamberale (1978) found a 3.7 fold difference in alveolar air at 300 ppm exposure for 30 minutes when comparing exercising subjects to resting exposure.

CLEAN CHANNEL ASSOCIATION:

Comments:

I am concerned with some of the AEGL values recommended by the AEGL Committee as they approach the Lower Explosive Level (LEL). The emergency response community has used 10%LEL as their action levels for many years. This safety margin takes into account the error of the instruments and the conditions under which these measurements are taken. The Incident Commander is reminded to re-evaluate any response actions that entry team members would take when levels are above the action level; using higher levels may place teams in dangerous environments without considering other options. I request the committee remove any value from the summary tables that are above 50% of the LEL.This will prevent emergency responders from erroneously assuming that these levels would not have potential lethal results. When derived values are above 50%of the LEL, the recommended numbers should not be within the summary tables but instead put in a footnote. Levels above 10%of the LEL can be within the tables with a footnote similar to that used for some of the published chemicals. Both Methyl Ethyl Ketone (MEK)and Xylene have this situation.

For Xylene, the 10-minute AEGL-3 value of 2,100 ppm is above 10% of the LEL for all forms of Xylene (o-xylene (9,000 ppm) and m-and p-xylene LEL (11,000 ppm)) and should be noted in all summary tables. Since the other AEGL 3 values are between 10% of the LEL for o-xylene and m-and p-xylene (11,000 ppm) an additional note should be added to enable emergency responders to draw their own conclusions.

Response: The suggested change has been made.

MICHIGAN DEQ

Comments:

The discussion in the Federal Register proposed rule and technical support document on xylenes was very good and quite complete. Many of the relevant toxicity studies were reviewed. However, this reviewer believes the documentation could be improved by including additional discussion concerning why an AEGL value is not developed for each of the individual xylene isomers. That is, discussion should include why one AEGL value should apply to all of the isomers and the mixture. For example, it could be mentioned that the individual isomers and mixture are expected to have similar toxicity, and metabolic pathways of each isomer proceeds via the same mechanism. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers.

> **Response: The description of the studies investigating the potential differences in the toxicity of the individual isomers that was included in the IRIS Xylenes document will be added to the AEGL document (see Appendix, this document), with the statement:**
>
> **"Only a limited number of studies were found in the searched literature comparing the toxicity of the individual xylene isomers. Although differences did exist among the isomers, no consistent, significant differences in the potency of the isomers following oral or inhalation exposure were identified. Additionally, metabolism of each isomer proceeds via the same pathways. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers."**

An additional comment concerns the use of the modeling to obtain AEGL 2 & 3 value for various shorter time periods. The selection of the NONMEM program for extrapolation to 10 and 30 minute exposure concentrations could use more discussion in the technical support document. Appendix B should describe in a general overview this software program for those unfamiliar with NONMEM. The following was obtained from the GloboMax® website, and could be paraphrased in the document to serve as an overview of NONMEM:

"GloboMax® LLC is pleased to announce its agreement with the Regents of University of California at San Francisco to become the licensor of NONMEM, the "gold standard" software package for Population Pharmacokinetic/ Pharmacodynamic data analyses. Since 1979, the NONMEM Project at the University of California at San Francisco has been concerned with the development of data analysis techniques and exportable software for estimating the parameters of nonlinear mixed effects (statistical regression-type) models. These techniques are particularly useful when the data are population pharmacokinetic/pharmacodynamic data, and when there are only a few PK/PD measurements from some individuals sampled from the population, or when the regression design varies considerably between individuals."

> **Response: If it is decided to continue to use the AEGL-2 and -3 values obtained by NOMEN, a reference to the software vendor wil be provided.**

AMERICAN CHEMISTRY COUNCIL

Comments:

The American Chemistry Council Toluene and Xylene Panel (the "Panel") appreciates the opportunity to submit the following comments on tehpropesed Acute Exposure Guideline Limits (AEGLs) for xylenes. The panel represents the major U.S. manufacturers of xylenes, which includes mixed xylenes, p-xylene, o-xylene, and m-xylene.

The Panel has reviewed proposed AEGL values presented in the July 18, 2003, Federal Register notice and the supporting document - the "Public Draft" of the Proposed AEGLs for Xylene May 2002 - that provide the detailed toxicology review and derivation of these proposed AEGLs. The toxicology review presented in the AEGL documentation appears to be thorough, organized, and well summarized. Further, the recommended critical studies and health endpoints used in deriving the AEGL-1, -2, and -3 values appear to be appropriate. The applied uncertainty factors and extrapolation for the time periods appear to be consistent with the established guidelines published in the SOP for Developing AEGLs for Hazardous Chemicals.

The Panel does, however, believe that the proposed AEGLs and the corresponding documentation should be revised to clearly indicate that these AEGLs apply to both mixed xylenes as well as to the individual isomers of xylene and any combination thereof. The toxicology assessment clearly covers the data on all three of the individual isomers in addition to data on mixed (technical) xylenes. Recent reviews by EPA for the IRIS database and by the OECD for it SIDS program have concluded that the individual isomers and mixed xylenes can be treated similarly for hazard and risk assessment. The toxicology and metabolism data presented in the proposed AEGL document also supports this conclusion.

Response: Same comment as that provided to MDEQ:

The description of the studies investigating the potential differences in the toxicity of the individual isomers that was included in the IRIS Xylenes document will be added to the AEGL document (see Appendix, this document), with the statement:

"Only a limited number of studies were found in the searched literature comparing the toxicity of the individual xylene isomers. Although differences did exist among the isomers, no consistent, significant differences in the potency of the isomers following oral or inhalation exposure were identified. Additionally, metabolism of each isomer proceeds via the same pathways. Therefore, the proposed xylene AEGL values apply to any of the xylene isomers or a mixture of xylene isomers."

The individual xylene isomers are produced primarily for use as intermediates in the production of other chemicals. As the Executive Summary does not address these applications, the Panel

suggest that the following passage, taken from the recent xylenes SIDS profile (May 2003), be included:

> *The primary use of the individual isomers is as chemical intermediates. Almost all o-xylene produced in the U.S. is consumed in the manufacture of phthalic anhydride. Other minor uses include the use of o-xylene as a feedstock in the production of bactericides, soybean herbicides, and dyes. Most m-xylene is used as a chemical intermediate in the production of isophthalic acid. Small amount of m-xylene are also consumed in the production of meta-tolic acid, isophthalonitrile, and other compounds, Almost all U.S. production of p-xylene is consumed in the manufacture of dimethyl terephthalate (DMT) and terephthalic acid (TPA), which are used in the production of polyester fiber and plastics.*

Response: This can be added.

Appendix - The description of the studies investigating the potential differences in the toxicity of the individual isomers

Moser et al. (1985) evaluated the effects of the individual xylene isomers and a commercial xylene mixture on operant responding and motor performance in CD-1 male albino mice following 30-minute static inhalation exposures. The minimally effective concentration for disruption of operant performance was 1400 ppm for all isomers, with an EC_{50} (concentration producing half-maximal decreases in response rate) of 6176, 5179, or 5611 ppm for m-xylene, o-xylene, and p-xylene, respectively. The operant response was biphasic, with concentrations of 1400 to 2400 ppm producing increased rates of response, and a concentration of 7000 ppm suppressing the response rate and also producing gross ataxia and prostration. The minimally effective concentrations for the inverted screen test were 3000 ppm for m- and o-xylene, and 2000 ppm for p-xylene, while the EC_{50} values for performance on the inverted screen test were 3790, 3640, and 2676 ppm for m-xylene, o-xylene, and p-xylene, respectively. Motor ability was recovered approximately 5 to 15 minutes after exposure. The study authors concluded that there was no consistent, significant difference in the potency of the individual isomers. While o-xylene exhibited a more potent effect on operant behavior, p-xylene more severely affected motor performance.

In a study by Molnár et al. (1986), motility was assessed in groups of eight, CFY white, male rats following exposure by inhalation for 4 hours to at least six concentrations each of m-xylene, o-xylene, or p-xylene (individual concentrations not provided). Exposure to 130 to 1500 ppm m-xylene and 400 to 1500 ppm p-xylene resulted in a concentration-related increase in group motility, while exposure to 150 to 1800 ppm o-xylene resulted in a slight depression of activity. At higher concentrations, however, activity was decreased in all groups, with the minimum narcotic concentration for the three isomers reported as 2180 ppm for o-xylene, 2100 ppm for m-xylene, and 1940 ppm for p-xylene.

Korsak et al. (1990) found that o-xylene more severely affected motor performance. Groups of ten, male Wistar rats were exposed to approximately 3000 ppm o-, m-, or p-xylene for six hours, with rotarod performance measured before and after termination of the exposure. The results of the testing given in terms of the number of failures/number of tested animals was as follows: o-xylene at average concentration of 3027 ppm was 19/20; m-xylene at average concentration of 3093 ppm was 6/20; p-xylene at average concentration of 3065 ppm was 1/20.

Condie et al. (1988) did not find any significant differences in the toxicity of the individual isomers in an experiment in which Sprague-Dawley rats were administered m-, o-, or p-xylene orally by gavage in corn oil for 10 consecutive days at doses of 0, 250, 1000, or 2000 mg/kg/day. Two female rats receiving the high-dose of p-xylene died and deaths were attributed to treatment. Male rats receiving 2000 mg/kg/day of each isomer had statistically lower body weights (88-94% of controls), while the body weights of high-dose females were not affected. Males and females receiving 2000 mg/kg/day of each isomer had statistically elevated liver weights and/or liver to body weight ratios (ranging from 128-148% of controls). Certain treatment groups also had decreased spleen or thymus weights. No treatment-related effects were observed in hematology,

clinical chemistry, or urinalysis parameters. The authors concluded that there were no significant differences in the toxicity of the individual isomers.

To address the potential for the 3 isomers to cause maternal or developmental toxicity, Ungváry et al. (1980) exposed groups of 15-30 pregnant, CFY rats to air containing measured concentrations of 35, 350, or 700 ppm of o-, m-, or p-xylene continuously during GD 7-14. Dams were sacrificed on GD 21. For a complete description of this study, the reader is referred to Section 4.3.2.2. Unfortunately, the usefulness of this study is limited because much of the actual data were not provided and the analyses of developmental toxicity was based on fetuses as the experimental unit instead of litters. The general conclusion is that m-xylene was the most toxic to the dams, while fetal toxicity varied with the isomer; for example, m-xylene resulted in decreased number of mean implantations/dam, p-xylene resulted in increased post implantation loss and corresponding decreased litter size, and all concentration of p-xylene and the highest concentration of o-xylene resulted in increased fetal incidence of skeletal retardation.

Fang et al. (1996) determined the Minimum Alveolar Concentration (MAC; the concentration that produces anesthesia, i.e. lack of movement, in 50% of those exposed) of the individual isomers in rats. The MAC of o-, m-, and p-xylene was 0.00118 ± 0.00009, 0.00139 ± 0.00010, and 00.00151 ± 0.0007 atm, respectively, with a difference of MAC values of less than 30% among the isomers.

Xylene is found in a number of consumer products, including solvents, paints or coatings, and as a blend in gasoline. Mixed xylenes are comprised of 3 isomers: m-xylene, o-xylene, and p-xylene, with the m-isomer predominating. Ethyl benzene is also present in the technical product formulation. Absorbed xylene is rapidly metabolized and is excreted almost exclusively in the urine as methylhippuric acid isomers in humans and as methylhippuric acid isomers and toluic acid glucuronides in animals. In both humans and animals, xylene causes irritation and effects the central nervous system following acute inhalation exposure. No consistent developmental or reproductive effects were observed in the studies found in the available literature. Commercial xylene and all 3 isomers have generally tested negative for genotoxicity. Xylenes are currently not classifiable as to its carcinogenicity by IARC or the U.S. EPA because of inadequate evidence.

The AEGL-1 is based upon the no-effect level was notable discomfort. Only slight eye irritation noted during a 30-minute exposure to 400 ppm mixed xylenes (Hastings et al., 1986). An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals ~~the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)~~. The resulting value of 130 ppm is supported by several other studies, including: a 150 ppm p-xylene exposure resulting in eye irritation in a contact lens wearer (Hake et al., 1981); a 15-minute exposure to 230 ppm mixed xylenes resulting in mild eye irritation and dizziness, but no loss of coordination, in one individual; and a 3-hour exposure to 200 ppm m- or p-xylene (Ogata et al., 1970), a 4-hour exposure to 200 ppm m-xylene (Savolainen et al., 1981), and a 5.5 hour exposure to 200 ppm m-xylene (Laine et al., 1993) all representing no-effect levels for notable discomfort.

The AEGL-2 is based upon the no effect level for the inability to escape. Poor coordination was observed ~~poor coordination resulting~~ when rats were exposed to 1300 ppm mixed xylenes for 4 hours (Carpenter et al., 1975). This concentration represents the threshold for reversible equilibrium disturbances and the no-effect level for the inability to escape. This concentration and endpoint are consistent with the preponderance of available data for 4-hour exposures in rats: the EC_{50} for decreased rotarod performance was 1982 ppm (Korsak et al., 1993); the minimum narcotic concentrations for m-,o-, and p-xylene ranged from 1940-2180 ppm (Molnár et al., 1986); and exposure to 1600 ppm p-xylene resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989), induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988). ~~In dogs, exposure to 1200 ppm for 4 hours represented a threshold for eye irritation (Carpenter et al., 1975)~~. An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and CNS depression results from the parent compound so there should be no substantial difference in response across species to an anaesthetic gas. An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in ~~greater~~ somewhat more rapid uptake of the chemical.

The AEGL-3 derivation is based upon the no effect level for lethality. Prostration, but no deaths occurred, ~~prostration occurring~~ in all 10 rats exposed for 4 hours to 2800 ppm mixed

xylenes, with recovery occurring within 1 hour of exposure (Carpenter et al., 1975). Although coordination initially remained poor, it returned to normal the following day. ~~This concentration also represents a no-effect level for lethality~~. An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D; PBPK modeling]), and a view of the data indicate little difference in interspecies sensitivity to xylene. Lethality data for mice and rats were nearly identical (Cameron et al., 1938; Bonnet et al., 1982), and death was preceded by narcosis that was likely the result of depression of the central nervous system resulting in respiratory arrest. A similar effect has been proposed for humans. Nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and central nervous system effects. An intraspecies uncertainty factor of 3 was applied because the MAC for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

The two primary effects of concern for xylene are those of irritation and central nervous system effects. Irritation is considered a threshold effect and therefore should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Pharmacokinetic modeling in both humans and rats indicate that venous blood concentrations rapidly increase during the first 15 minutes of exposure, followed by minimal increases in blood concentrations with continuing exposure (i.e., increases follow a hyperbolic curve). Likewise, available human data indicate that once the initial increase in blood xylene concentration is reached, blood concentrations level off with increasing exposure duration. Conversely, available human and animal data demonstrate that increasing exposure concentrations correlate with increases in venous blood xylene concentrations. Therefore, the AEGL 2- and -3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

The AEGL values should be protective of human health. The AEGL-1 values are consistent with other human studies, and represent a value consistent with exposure concentrations that might result in mild eye irritation. The AEGL-2 levels are protective, especially when considering numerous human studies investigating the effects of exposure to 200 ppm xylene with 20-minute peak exposures to 400 ppm, in some cases additionally combining peak exposures with physical exercise resulting in greater uptake of the chemical, and finding only minimal central nervous system effects. The difficultly in defining an AEGL-2 level for xylene comes from its "all-or-nothing" continuum of toxicity: toxicity ranges from mild irritation to narcosis, with little happening in between. The AEGL-3 levels represent the threshold for narcosis, and are protective as supported by human data demonstrating that exposure to 690 ppm for 15 minutes resulted in lightheadedness/dizziness and a 30 minute exposure to 700 ppm resulted in nausea, vomiting, dizziness or vertigo.

The proposed values are listed in the tables below.

Summary of Proposed AEGL Values for Xylenes [ppm (mg/m³)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	130 (560)	130 (560)	130 (560)	130 (560)	130 (560)	No effect level for notable discomfort. Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 minutes (Hastings et al., 1986)
AEGL-2 (Disabling)	990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)	No effect level for inability to escape. Rats exposed to 1300 ppm mixed xylenes for 4 hours exhibited poor coordination (Carpenter et al., 1975)
AEGL-3 (Lethal)	2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)	No effect level for lethality. Rats exposed to 2800 ppm for 4 hours exhibited prostration followed by a full recovery (Carpenter et al., 1975)

Add footnote for explosion level and asterisk those values exceeding 10% of the LEL

References

Bushnell, P.J. 1989. Behavioral effects of acute p-xylene inhalation in rats: Autoshaping, motor activity, and reversal learning. *Neurotoxicology and Teratology* 10: 569-577.

Bushnell, P.J., and Peele, D.B. 1988. Conditioned flavor aversion induced by inhaled p-xylene in rats. *Neurotoxicology and Teratology* 10: 273-277.

Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975b. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. *Toxicology and Applied Pharmacology* 33: 543-58.

Dyer, R.S., Bercegeay, M.S., and Mayo, L.M. 1988. Acute exposures to p-xylene and toluene alter visual information processing. *Neurotoxicology and Teratology* 10: 147-153.

Hake, C.R.L., Stewart, R.D., Wu, A., et al. 1981. p-Xylene: Development of a biological standard for the industrial worker. Report to the National Institute for Occupational Safety and Health, Cincinnati, OH, by the Medical College of Wisconsin, Inc., Milwaukee, WI. PB82-152844.

Hastings, L., Cooper, G.P., and Burg, W. 1986. Human sensory response to selected petroleum hydrocarbons. In: MacFarland, H.N. ed. Advances in Modern Environmental Toxicology. Vol. VI. Applied Toxicology of Petroleum Hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, pp. 255-270.

Korsak, Z., Swiercz, R., and Jedrychowski, R. 1993. Effects of acute combined exposure to – *n*-butyl alcohol and *m*-xylene. *Polish Journal of Occupational Medicine and Environmental Health* 6: 35-41.

Laine, A., Savolainen, K., Riihimäki, V., et al. 1993. Acute effects of m-xylene inhalation on body sway, reaction times, and sleep in man. *International Archives of Occupational and Environmental Health* 65: 179-188.

Molnár, J., Paksy, K.Á., and Náray, M. 1986. Changes in the rat's motor behavior during 4-hr inhalation exposure to prenarcotic concentrations of benzene and its derivatives. *Acta Physiologica Hungarica* 67: 349-354.

Ogata, M., Tomokuni, K., and Takatsuka, Y. 1970. Urinary excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene as a test of exposure. *British Journal of Industrial Medicine* 27: 43-50.

Savolainen, K., Riihimäki, V., Laine, A., and Kekoni, J. 1981. Short-term exposure of human subjects to m-xylene and 1,1,1-trichloroethane. *International Archives of Occupational Environmental Health* 49: 89-98.

4.4. Other Relevant Information

4.4.1. Interspecies Differences

Pharmacokinetic data in humans and rats were available for xylene isomers (see section 4.1). A comparison of the blood:air partition coefficients in humans and rats suggest that small rodents will experience greater systemic uptake than humans. The values for the human blood:air partition coefficient are 26.4, 31.9, and 32.5 for m-xylene; 31.1, 35.2, 34.9 for o-xylene; and 37.6, 39.0, and 44.7 for p-xylene (Sato and Nakajima, 1979; Pierce et al., 1996; Gargas et al., 1989), and the values for the rat blood:air partition coefficient are 46.0 for m-xylene; 44.3 for o-xylene, and 41.3 for p-xylene (Gargas et al., 1989).

The interspecies factor is comprised of the pharmacodynamic component as well. A view of the data indicate little difference in interspecies sensitivity to xylene. Lethality data for mice and rats were nearly identical (Cameron et al., 1938; Bonnet et al., 1982). Death was preceded by narcosis and was likely the result of depression of the central nervous system resulting in respiratory arrest. A similar effect has been proposed for humans. Nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and central nervous system effects.

4.4.2. Intraspecies Differences

All available data point to a 2-3-fold difference in interindividual sensitivity to xylenes.

Xylene acts as an anesthetic (Fang et al., 1996). Studies indicate that children, and particularly infants, are more resistant than adults to the effects of various volatile anesthetics (Gregory et al., 1969; Katoh and Ikeda et al., 1992; Lerman et al., 1983; Matthew et al., 1996; Stevens et al., 1975; LeDez and Lerman, 1987). The susceptibility of individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lung which produce "anesthesia" (i.e., lack of movement) have been measured. Values are usually reported as the Minimum Alveolar Concentration (MAC) which produces lack of movement in 50% of persons exposed to that concentration. MAC's for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitive (highest MAC values) occur in older infants, toddlers, and children as compared to normal adults. The total range of sensitivity is 2-3 fold. On the basis of this knowledge, it is not unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for xylenes.

Exercise has been found to increase alveolar and blood levels of xylenes during exposure (Gamberale et al., 1978; Riihimaki et al., 1979). Using a physiologically-based pharmacokinetic model for m-xylene in humans to assess various interindividual factors in determining the internal dose, Kaneko et al. (1991) reported that physical activity (50W) during a simulated 8-hour exposure to 50 ppm resulted in a 2.5-fold increase in blood concentration when compared to exposure at rest.

Fang et al. (1996) determined the MAC in rats of the individual isomers. The MAC of o-, m-, and p-xylene was 0.00118 ± 0.00009, 0.00139 ± 0.00010, and 00.00151 ± 0.0007 atm, respectively, with a difference of MAC values of less than 30% among the isomers.

4.4.3. Concentration-Exposure Duration Relationship

The two primary effects of xylene exposure are those of irritation and central nervous system effects. Irritation is considered a threshold effect and therefore should not vary over time. An AEGL value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

The central nervous system effects of xylene are attributed to the low molecular weight and lipophilic nature of xylene allowing the solvent to readily cross the blood:brain barrier (see section 4.2). Distribution studies of xylene following inhalation exposures have confirmed high concentrations of xylene in the brain and central and peripheral nervous system immediately after exposure, with elimination often occurring by 1 hour post exposure. The rapid onset of central nervous system effects combined with the transient nature of the xylene-induced nervous system disturbances is likely attributable to direct interaction of the chemical with the central nervous system followed by the rapid elimination of xylene. Based on the above information, the xylene-blood concentration will be a key determinant in central nervous system effects. Pharmacokinetic modeling in both humans and rats indicate that venous blood concentrations rapidly increase during the first 15 minutes of exposure, followed by minimal increases in blood concentrations with continuing exposure (i.e., increases follow a hyperbolic curve) (Tardif et al., 1993; 1995). Likewise, available human data indicate that once the initial increase in blood xylene concentration is reached, blood concentrations level off with increasing exposure duration (see Table 11) (Hake et al., 1981; Savolainen et al., 1980; 1981; 1985b). Conversely, available human and animal data demonstrate that increasing exposure concentrations correlate with increases in venous blood xylene concentrations (Hake et al., 1981; Tardif et al., 1993; Laine et al., 1993). These data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL values based upon central nervous system effects are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix 2).

TABLE 11. Relationship Between Xylene Exposure Concentration (In Air) and Blood Xylene Concentration in Human Volunteers

Exposure concentration (ppm)	Number of subjects	Time into exposure (h)	Venous blood xylene concentration	Comments	Reference
100*	8	1	18.4 ± 5.3 (μmol/L)	m-Xylene, odor masked with peppermint oil	Savolainen et al., 1980
		1.67	13.3 ± 2.2		
		2	21.6 ± 6.3		
		3	13.4 ± 2.9		
200*	9	0.25	16.6 ± 4.8 (μmol/L)	m-Xylene, odor masked with peppermint oil	Laine et al., 1993
		0.33	17.3 ± 5.5		
		0.67	21.3 ± 5.4		
		2	28.5 ± 5.2		
200	6	1.17	24.9 ± 2.1 (μmol/L)	m-Xylene, odor masked with peppermint oil (<1.0 ppm)	Savolainen et al., 1981
		2.5	26.7 ± 3.4		
		3.75	28.6 ± 3.5		
20	1	1	0.24 (ppm; w/w)	p-Xylene, Subjects were sub-divided into 3 daily groups for 1, 3, or 7.5 hour-long exposures. Males were exposed to 100 ppm for the 1st week (5 days/week), 20 ppm the 2nd week, and 150 ppm the 3rd week. Values reported are for the first exposure day of each new week.	Hake et al., 1981
	2	3	0.41 ± 0.09		
	3	7.5	0.42 ± 0.03		
100	2	1	1.23 ± 0.18		
	2	3	1.65 ± 0.50		
	4	7.5	1.29 ± 0.21		
150	2	1	2.04 ± 0.76		
	2	3	3.18 ± 0.11		
	4	7.5	3.86 ± 0.65		

* Exposure protocol was: 3 hour exposure in the morning, 40 minute break for lunch, followed by exposure for 1 or 3 hours in afternoon. Only values for continuous exposure in the morning session are reported.

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

Exposure to 100, 200 or 400 ppm mixed xylenes for 30 minutes resulted in nonstatistically increased incidences of eye irritation; no nose or throat irritation were noted and no changes in behavioral tests or respiratory measurements were evident (Hastings et al., 1986). That the eye irritation was mild is supported by observation that the number of eye blinks/minute were not affected by exposure. Exposure to 100 or 150 ppm p-xylene for 7.5 hours/day, 5 days/week resulted only in mild eye irritation, most often in one male wearing contact lenses (irritation was noted on the first exposure day) (Hake et al.,1981). No effects on performance tests were observed. Exposure to 110 ppm mixed xylenes for 15 minutes resulted in intermittent, mild throat irritation in 1/6 individuals, while exposure to 230 ppm mixed xylenes for 15 minutes resulted in eye irritation and mild dizziness in 1/7 individuals (Carpenter et al., 1975b).

A number of controlled human exposures reported no effects following exposure to xylenes. Exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours did not effect blood pressure, pulse rate, flicker value, or reaction time (Ogata et al., 1970). Olson et al. (1985) found exposure to 70 ppm p-xylene for 4-hours did not effect choice reaction time, simple reaction time, short term memory, heart rate, or subjective symptoms in exposed volunteers. No adverse effects on visual evoked potential, tapping speed, body sway, reaction time, or critical flicker fusion were measured in volunteers exposed to 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1983). Body sway, reaction times, and active or quiet sleep were not effected by exposure to 200 ppm for 5.5 hours (Laine et al., 1993).

5.2. Animal Data Relevant to AEGL-1

No effects were observed in dogs exposed to 530 ppm or in rats exposed to 580 ppm mixed xylenes for 4 hours (Carpenter et al., 1975b). Lacrimation in dogs and poor coordination in rats were observed at the next higher exposure concentrations of 1200 ppm and 1300 ppm, respectively (Carpenter et al., 1975b).

5.3. Derivation of AEGL-1

The AEGL-1 is based upon the no-effect level was notable discomfort. Only slight eye irritation noted in the Hastings et al. (1986) study during a 30-minute exposure to 400 ppm mixed xylenes. The effect level for notable discomfort is suggested to be 690 ppm (Carpenter et al., 1975a). At this exposure none of the individuals thought that thires exposure could be tolerated over an 8-hour workday. The Hastings et al. (1986) study was chosen because the exposure was to mixed xylenes as opposed to individual isomers, and the exposure concentration represented a concentration at which an effect was observed, i.e., that of mild eye irritation. An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals ~~the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort)~~. Because irritation is considered a threshold effect and should therefore not vary over time, the threshold value is applied to all times. AEGL-1 values are presented in Table 12.

TABLE 12. AEGL-1 Values for Xylenes [ppm (mg/m³)]				
10-minute	30-minute	1-hour	4-hour	8-hour
130 (560)	130 (560)	130 (560)	130 (560)	130 (560)

The 130 ppm value is supported by several other studies, including: the 150 ppm p-xylene exposure resulting in eye irritation in a contact lens wearer (represents sensitive population; Hake et al., 1981); the 15-minute exposure to 230 ppm mixed xylenes resulting in mild eye irritation and dizziness in one individual; and the 3-hour exposure to 200 ppm m- or p-xylene (Ogata et al., 1970), the 4-hour exposure to 200 ppm m-xylene (Savolainen et al., 1981), and the 5.5 hour exposure to 200 ppm m-xylene (Laine et al., 1993), all representing no-effect levels for notable discomfort.

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

One of six or seven individuals noted dizziness during a fifteen minute exposure to 230 ppm (during the last 2 minutes of exposure) or 460 ppm mixed xylenes (starting at the 6th minute and continuing to the end of exposure; same individual), while a 15-minute exposure to 690 ppm mixed xylenes resulted in dizziness/lightheadedness in 4/6 individuals (Carpenter et al., 1975b). In the same study, a 15-minute exposure resulted in eye irritation in 1/7, 4/6 and 4/6 individuals exposed to 230, 460, or 690 ppm mixed xylene, respectively.

6.2. Animal Data Relevant to AEGL-2

Exposure to 1200 ppm or 1300 ppm mixed xylenes for 4 hours represents a threshold for lacrimation in dogs and poor coordination (reversible) in rats, respectively (Carpenter et al., 1975b). The 4-hour m-xylene EC_{50} for decreased rotarod performance in rats was 1982 ppm (Korsak et al., 1993), and the 4-hour minimum narcotic concentrations for the 3 xylene isomers in rats ranged from 1940-2180 ppm (Molnar et al., 1986). Exposure of rats to 1600 ppm p-xylene for 4-hours resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989), induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988).

Following 30-minute static exposures in mice, Moser et al., (1985) determined the EC_{50} for decreased performance on the inverted screen test to be 3790 ppm for m-xylene, 3640 ppm for o-xylene, and 2676 ppm for p-xylene, while the EC_{50} for disruption of operant performance was 6176 ppm for m-xylene, 5179 ppm for o-xylene, and 5611 ppm for p-xylene.

6.3. Derivation of AEGL-2

The AEGL-2 is based upon the no effect level for the inability to escape. Poor coordination was observed ~~poor coordination resulting~~ when rats were exposed to 1300 ppm mixed xylenes for 4-hours (Carpenter et al., 1975b). This concentration represents the threshold for reversible equilibrium disturbances and the no-effect level for the inability to escape. This concentration and endpoint are consistent with the preponderance of available data for 4-hour

exposures in rats: the EC_{50} for decreased rotarod performance was 1982 ppm (Korsak et al., 1993); the minimum narcotic concentrations for m-, o-, and p-xylene ranged from 1940-2180 ppm (Molnar et al., 1986); and exposure to 1600 ppm p-xylene resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989)~~, induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988). In dogs, exposure to 1200 ppm for 4 hours represented a threshold for eye irritation (Carpenter et al., 1975b)~~. These exposures are effect levels for the inability to escape.

An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and a view of the data indicate little difference in interspecies sensitivity to xylene (see Section 4.4.1). An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity (see Section 4.4.3). Therefore, the AEGL-2 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix B).

AEGL-2 values are presented in Table 13.

TABLE 13. AEGL-2 Values for Xylenes [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)

The human data reported by Carpenter et al. (1975b) were not used for the AEGL-2 derivation because the exposure duration was for only a short time (15 minutes) and because it not consistent with the preponderance of human data from other controlled human exposures. If one were to use the highest exposure concentration (690 ppm which resulted in eye irritation and dizziness in 4/6 individuals; threshold for equilibrium effects) and apply the intraspecies uncertainty factor of 3, one obtains a value of 230 ppm. This concentration is supposed to represent a concentration at which exposed individuals could experience irreversible or other serious, long-lasting adverse health effects, or have an impaired ability to escape. However, a number of studies demonstrate that only minor sensory irritation is observed ~~this concentration has no adverse effects upon exposed individuals: no adverse effects were observed~~ following exposure to 100 or 200 ppm m- or p-xylene for 3 or 7 hours (Ogata et al., 1970); 200 ppm m-xylene for 4 hours (Savolainen et al., 1981; Seppalainen et al., 1985), or 200 ppm for 5.5 hours (Laine et al., 1993).

Additionally, numerous human studies investigated the effects of exposure to: 200 ppm m-xylene with 20 minute peaks of 400 ppm (Seppalainen et al., 1989; 1991; Laine et al., 1993;

Savolainen and Linnavuo, 1979); 135 ppm m-xylene with 20 minute peaks of 400 ppm (Savolainen et al., 1984; 1985a; 1985b); or 140 ppm m-xylene with 10 minute peaks of 400 ppm (Riihimaki and Savolainen, 1980; Savolainen and Riihimaki, 1981). The studies also combined peak exposures with exercise, thereby increasing the uptake of the chemical. These studies found either no effect; or ~~reported~~ only minimal central nervous system effects.

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

Morley et al. (1970) reported the cases of 3 individuals exposed to approximately 10,000 ppm xylene for approximately 18 hours. One individual died, while the other two individuals were found unconscious but experienced a full recovery.

7.2. Animal Data Relevant to AEGL-3

Two cats exposed to 9500 ppm mixed xylenes exhibited central nervous system effects followed by death 2 hours into the exposure (Carpenter et al., 1975b). In rats, 4-hour LC_{50}s values for mixed xylenes have been reported as 6350 ppm (Hine and Zuidema, 1970), 6011 ppm (Carpenter et al., 1975b), and 11,000 ppm (Lundberg et al., 1986), and for p-xylene as 4645 ppm (Harper et al., 1975). Six-hour LC_{50} values for the m-, o-, and p-isomers were 5984, 4330, and 4591 ppm in rats, respectively, and 5267, 4595, and 3907 ppm in mice, respectively (Bonnet et al., 1979; 1982).

A no-effect level for death in rats following exposure to mixed xylenes for 4 hours was 2800 ppm (Carpenter et al., 1975b). Clinical signs observed during exposure to 2800 ppm included prostration between 2-3.5 hours into the exposure. Recovery occurred within 1-hour post exposure, but coordination remained poor until the following day. At the next lower concentration of 1300 ppm, poor coordination was noted 2 hours into the exposure, with coordination returning to normal after the exposure. Molnar et al. (1986) reported 4-hour minimum narcotic concentrations of 2100, 2180, and 1940 ppm for the m-, o-, and p-xylene isomers, respectively.

RD_{50} values in mice were 1467 ppm for o-xylene (De Ceaurriz et al., 1981), 1361 ppm for m-xylene (Korsak et al., 1993), and 2440 ppm for mixed xylenes (Korsak et al., 1988). It should be noted, however, that Korsak et al. (1993; 1988) did not use the recommended strain of mice.

7.3. Derivation of AEGL-3

The AEGL-3 derivation is based upon the no effect level for lethality. Prostration, but no deaths occurred, ~~prostration occurring~~ in all 10 rats exposed for 4 hours to 2800 ppm mixed xylenes, with recovery occurring within 1 hour of exposure (Carpenter et al., 1975b) Although coordination initially remained poor, it returned to normal the following day. ~~This concentration also represents a no-effect level for lethality.~~

An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans (see Appendix D [PBPK modeling]), and a view of

the data indicate little difference in interspecies sensitivity to xylene (see Section 4.4.1). An intraspecies uncertainty factor of 3 was applied because the MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity (see Section 4.4.3). Therefore, the AEGL-3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes (see Appendix B).

AEGL-3 values are presented in Table 14.

TABLE 14. AEGL-3 Values for Xylenes [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)

Available data indicated that these values should be protective of human health. A 15-minute exposure to 690 ppm for 15 minutes resulted in eye irritation and dizziness and/or lightheadedness (Carpenter et al., 1975b), and a 30 minute exposure to concentrations as high as 700 ppm xylene resulted in headache, nausea, vomiting, dizziness or vertigo, eye irritation, or nose or throat irritation (Klaucke et al., 1982).

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

The proposed AEGL values for xylenes are summarized in Table 15.

TABLE 15. Summary/Relationship of AEGL Values [ppm(mg/m^3)]

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	130 (560)	130 (560)	130 (560)	130 (560)	130 (560)
AEGL-2 (Disabling)	990 (4300)	480 (2100)	430 (1900)	430 (1900)	430 (1900)
AEGL-3 (Lethal)	2100 (9100)	1000 (4300)	930 (4000)	930 (4000)	930 (4000)

APPENDIX B: Time-Scaling Calculations

Derivation of AEGL-2 (10 minutes and 30 minutes)

Because the key study for the AEGL-2 derivation is a study with a 4-hour exposure duration, extrapolation to shorter time periods was necessary. It was decided to use a toxicokinetic approach to calculate AEGL-2 values for 10 minutes and for 30 minutes.

The following assumptions were made:

(i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 430 ppm for 4 hours
(ii) it is the concentration and not the amount of the substance (AUC) which is responsible for the effect, qualitatively and quantitatively
(iii) the data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
(iv) the data of m-xylene were used to represent the mixture of all xylenes
(v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model described the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated, the input rate to reach this concentration with 10 minutes and 30 minutes, respectively, was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

The outcome of the calculations was as follows: k which is the first order elimination constant was 2.74/ hour; the corresponding half life is 0.25 hours. The concentration at 4 hours was 6.5 ± 10 mmol/L (mean ±2 SD) for 430 ppm. The external air concentration to reach this concentration within 10 minutes is 1165 ±180 ppm (mean ±2 SD) and within 30 minutes is 570±87.5 (mean±2 SD).

Calculating the lower boundary value for 2 SD results in
10 min: 985 ppm
30 min: 482.5 ppm

Calculating the lower boundary value for 3 SD results in
10 min: 896 ppm
30 min: 438.4 ppm
Please see Figure.

conc (mmol/L)	65 (mean)	55 (-2 SD)	50 (-3 SD)
10 min	1165 ppm	985 ppm	896 ppm
30 min	570 ppm	483 ppm	438 ppm

Derivation of AEGL-3 (10 minutes and 30 minutes)

Because the key study was a study with a 4-hour exposure duration, extrapolation to shorter time periods was necessary. It was decided to use a toxicokinetic approach to calculate AEGL-3 values for 10 and for 30 minutes.

The following assumptions were made:

(i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 930 ppm for 4 hours
(ii) it is the concentration and not the amount of the substance (Auc) which is responsible for the effect, qualitatively and quantitatively
(iii) the data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
(iv) the data of m-xylene were used to represent the mixture of all xylenes
(v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

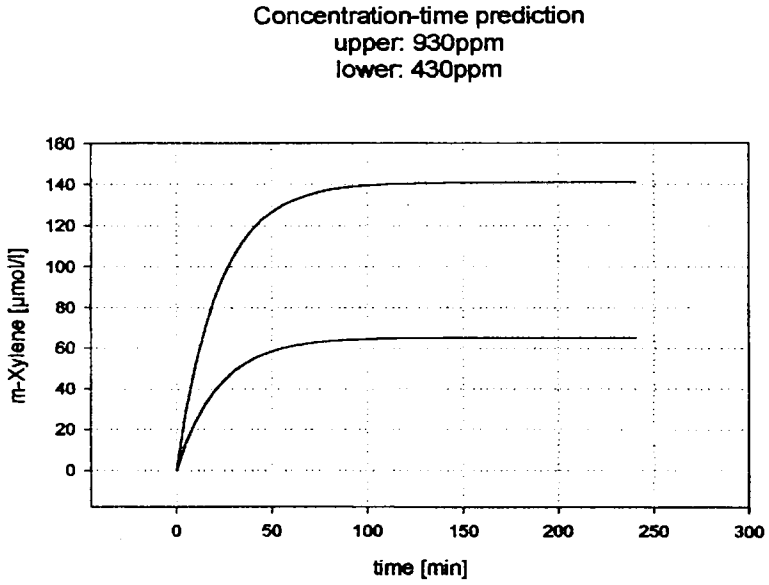
Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model described the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated, the input rate to reach this concentration within 10 minutes and 30 minutes, respectively, was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

The outcome of the calculations was as follows: k which is the first order elimination constant was 2.74/hour; corresponding half life is 0.25hours. The concentration at 4 hours. was 141 ± 25 mmol/L (mean ± 2 SD) for 930 ppm. The external air concentrations to reach this concentration within 10 minutes is 2526 ± 455 ppm (mean ± 2SD) and within 30 minutes is 1237 ± 221 ppm (mean ± 2 SD).

Calculating the lower boundary value for 2 SD results in
10 min: 2071 ppm
30 min. 1016 ppm

Calculating the lower boundary value for 3 SD results in
10 min: 1790 ppm
30 min: 963 ppm
Please see Figure.

conc (mmol/L)	141 (mean)	116 (-2 SD)	103.5 (-3 SD)
10 min	2526 ppm	2071 ppm	1790 ppm
30 min	1237 ppm	1016 ppm	963 ppm


Concentration-time prediction
upper: 930ppm
lower: 430ppm
m-Xylene [µmol/l]
160
140
120
100
80
60
40
20
0
0
50
100
150
200
250
300
time [min]

APPENDIX C: Derivation Summary for Xylene AEGLs

ACUTE EXPOSURE GUIDELINES FOR XYLENES CAS Reg. No. 1330-20-7 DERIVATION SUMMARY

AEGL-1 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
130 ppm	**130 ppm**	**130 ppm**	**130 ppm**	**130 ppm**

Key Reference: Hastings, L., Cooper, G.P., and Burg, W. 1986. Human sensory response to selected petroleum hydrocarbons. In: MacFarland, H.N. ed. Advances in Modern Environmental Toxicology. Vol. VI. Applied Toxicology of Petroleum Hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, pp. 255-270.

Test Species/Strain/Number: Volunteer human male

Exposure Route/Concentrations/Durations: Subjects were exposed by inhalation via an olfactometer delivery hood to 0, 100, 200, or 400 ppm mixed xylene for 30 minutes

Effects: Mild eye irritation reported by 56, 60, 70, and 90% of subjects exposed to 0, 100, 200, or 400 ppm mixed xylene, respectively; no effects observed on behavioral test results

Endpoint/Concentration/Rationale: Mild eye irritation was noted by 90% of the subjects exposed to 400 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - human data used
Intraspecies: 3 - the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort).

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA - human data used

Time Scaling: Irritation is considered a threshold effect and therefore should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data Adequacy: This was an acceptable study, but could have been improved had the number of volunteers been reported. However, the data are consistent with other human studies, and represent a value consistent with exposure concentrations that might result in mild eye irritation.

AEGL-2 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
990 ppm	**480 ppm**	**430 ppm**	**430 ppm**	**430 ppm**

Key Reference: Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33: 543-58.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old/group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to 580, 1300, 2800, 4000, or 9000 ppm mixed xylene for 4 hours

Effects:

Conc.(ppm)	Mortality	Other effects
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate between 2-3.5 hours recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 minutes; all survivors prostrate but recovered promptly
9900	10/10	none stated

Endpoint/Concentration/Rationale: Exposure to 1300 ppm for 4 hours resulted in poor coordination

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans.
Intraspecies: 3 - The MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL-2 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

Data Adequacy: This was a well-designed and conducted study. The data are supported by numerous other studies in rats, as well as a study in dogs. The AEGL-2 levels are protective of human health, especially when considering numerous human studies investigated the effects of exposure to 200 ppm xylene with 20-minute peak exposures to 400 ppm, in some cases additionally combining peak exposures with physical exercise resulting in greater uptake of the chemical, and found only minimal central nervous system effects.

AEGL-3 VALUES				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
2100 ppm	**1000 ppm**	**930 ppm**	**930 ppm**	**930 ppm**

Key Reference: Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33: 543-58.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old/group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to 580, 1300, 2800, 4000, or 9000 ppm mixed xylene for 4 hours

Effects:

Conc.(ppm)	Mortality	Other effects
580	0/10	none observed
1300	0/10	poor coordination after 2 hours, returned to normal
2800	0/10	irritation; all rats prostrate between 2-3.5 hours recovered within 1 hr, coordination returned to normal next day
6000	4/10	rats prostrate within 30 minutes; all survivors prostrate but recovered promptly
9900	10/10	none stated

Endpoint/Concentration/Rationale: Exposure to 2800 ppm for 4 hours resulted in prostration followed by full recovery

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 - An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans.
Intraspecies: 3 - The MAC (minimum alveolar concentration) for volatile anesthetics should not vary by more than a factor of 2-3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA

Time Scaling: Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Therefore, the AEGL- 3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

Data Adequacy: This was a well-conducted study. The AEGL-3 levels are supported by human data demonstrating that exposure to 690 ppm for 15 minutes resulted in lightheadedness/dizziness and a 30 minute exposure to 700 ppm resulted in nausea, vomiting, dizziness or vertigo.

PBPK Modeling of Xylenes

Claudia M. Troxel
Jim Dennison, Colorado State University
Harvey Clewell, ENVIRON International Corp.

Why Modeling?

- Previous suggestions from COT to use PBPK modeling in AEGL determinations.
- PBPK models were used to estimate brain and blood concentrations at LC_{50} for various VOCs. They found that some of variation in LC_{50} values was due to toxicokinetics. For 12 of 15 VOCs, the Cv* at the LC_{50} ranged from 2.0 - 9.5 mM, whereas the LC_{50}s ranged from 2,965 - 129,000 ppm (DeJongh et al., 1998).
- The AEGL-2 and -3 key study used 4-h exposure duration: extrapolation to shorter time periods necessary

• Cv = venous blood concentration

Summary of proposed AEGL values for Xylenes					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	130	130	130	130	130
AEGL-2	990	480	430	430	430
AEGL-3	2100	1000	930	930	930

AEGL-1: Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 min. (Hastings et al., 1986)

AEGL-2: Rats exposed to 1300 ppm mixed xylenes for 4 h exhibited poor coordination (Carpenter et al., 1975)

AEGL-3: Rats exposed to 2800 ppm for 4 h exhibited prostration followed by full recovery (Carpenter et al., 1975)

Current 10 and 30 m AEGL-2 and -3 extrapolation:

One compartment model; used NOMEN program
Following assumptions made:

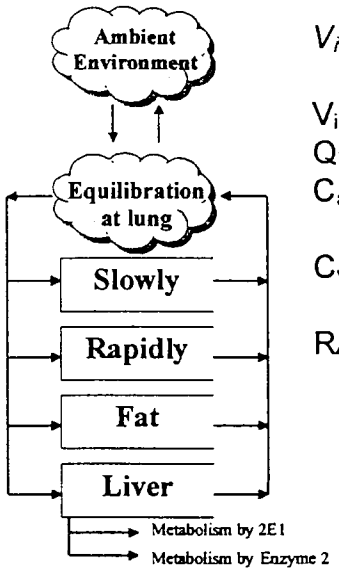
- toxicological endpoint and intensity of toxicological effect should be same as observed after admin. of 430 ppm for 4 h
- it is concentration and not amount of the substance (AUC) responsible for the effect, qualitatively and quantitatively
- data from kinetic studies in human volunteers (see Table 11, page 37) are appropriate for further kinetic calculations
- the data of m-xylene were used to represent the mixture of all xylenes
- the kinetics of m-xylene are linear in the concentration/ dose range which is under consideration.
- assumed inhalation volume and frequency being constant

PBPK Model Specifics:

- Basically only one xylene model published, and it was for the single isomer m-xylene. A series of publications were generated by the Krishnan and Tardif research group, with the main differences among the models being the physiological parameters used.
- We coupled the model with additional human data from four different publications for verification.
- We then ran the rat model to determine Cv (venous blood concentration) for the AEGL endpoint. We next ran the human model for each time period to determine the equivalent exposure producing the same Cv.

What We Used:

- A standard 4 compartment model.
- Tardif, et al., 1993.
  gas-uptake data in rats: 500, 1000, 2000, 4000 ppm
- Tardif et al., 1997.
  Cv in rats following 4 hr exposure to 100 or 200 ppm
- Haddad et al., 1999.
  Added Cv in rats following 4 h exposure to 50 ppm
  Metabolism parameters except as noted
  Partition parameters (from Gargas 1987 et al. (in vitro))
- Tissue flows and volumes are standard parameters values used in modeling, generally from Brown et al.



$V_i dC_i/dt = Q_i(C_a - C_{vi})$ - RAM

Where

V_i = tissue volume (L)

Q_i = tissue perfusion rate (L/h)

C_a = concentration of solvent in the systemic arterial blood (mg/L)

C_{vi} = concentration of solvent in venous blood leaving tissue, i (mg/L)

RAM = rate of change in the amount metabolized

RAM = AMS + AML

$RAMS = V_{max} \times C_{VL}/(K_m + C_{VL})$

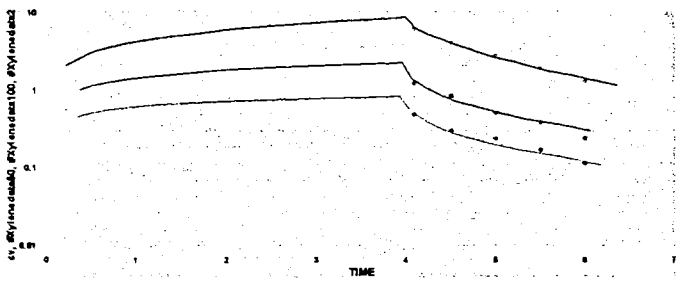
$RAML = KF * C_{VL}$

(KF = 1st order rate constant for high-capacity/low affinity enzymes)

Haddad 1999 Rat Model:

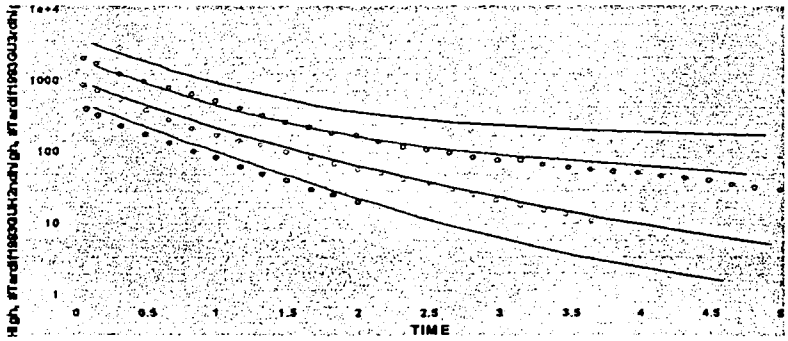
We chose the 1999 model over 1997 model because 1999 model was second version, more data rich, and fit slightly better. Was not a large difference between them.

Does have limitation that was in SD rats and only had post exposure data at xylene concentrations up to 200 ppm.



Model Using Tardif's Gas Uptake Data:

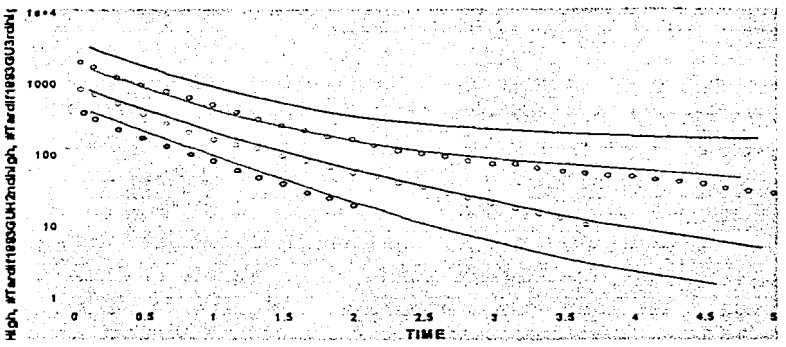
In the Haddad 1999 model, slightly different parameters used for tissue volumes and metabolism compared to Tardif 1993 model. We ran the 1999 model with the 1993 gas uptake data (500, 1000, 2000, 4000 ppm). The results suggest that the 1993 and 1999 models are essentially the same since the plot shown here is essentially the same as in the 1993 paper. At the lower concentrations, the model would actually fit perfectly if they adjust the starting concentration to what shows. Note: acute lethality critical study was at exposure level between the 2nd and 3rd doses here.



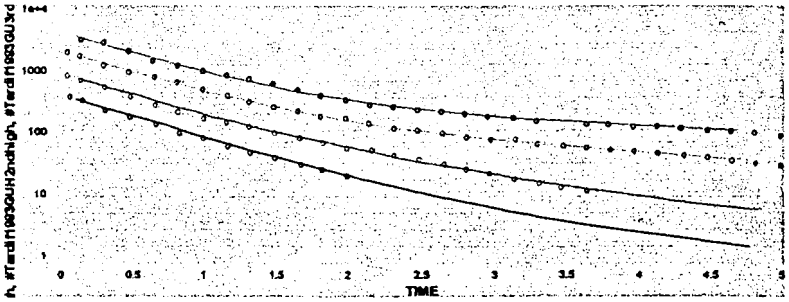
So, using same model, we optimized starting concentrations to reflect first data points.

Also, saw that we needed to include a 2nd pathway of metabolism - (lumped metabolism by all of CYPs other than CYP2E1; account for high capacity/low affinity pathways of metabolism). The metabolism by second series of CYP is given as:
*rate of metabolism (RAM) = KF * C_{VL} where*
*KF = 0.1/BW**0.3*

Added the second pathway and determined KF (1st order rate constant for high-capacity/low affinity enzymes).

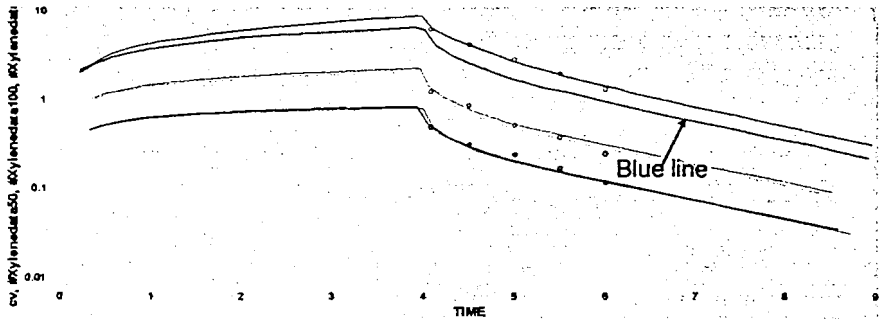


Unchanged from Tardiff paper

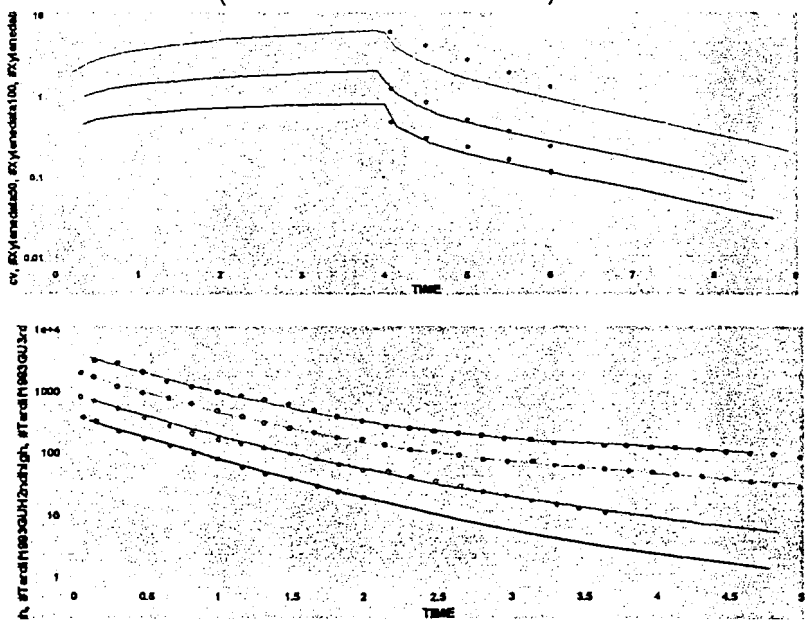


Optimized starting conc.; included 2nd metabolism pathway

Reran the model with all the same parameters against the Haddad data. A good fit is obtained overall, although the 200 ppm is underpredicted a little. However, we are mostly concerned with estimating C_V in rats at very high concentrations (1,000 to 3,000 ppm). This figure shows what the model does without linear pathway (perfect fit) and with it. No real difference at 50, 100 ppm, but the blue line is the new model at 200.

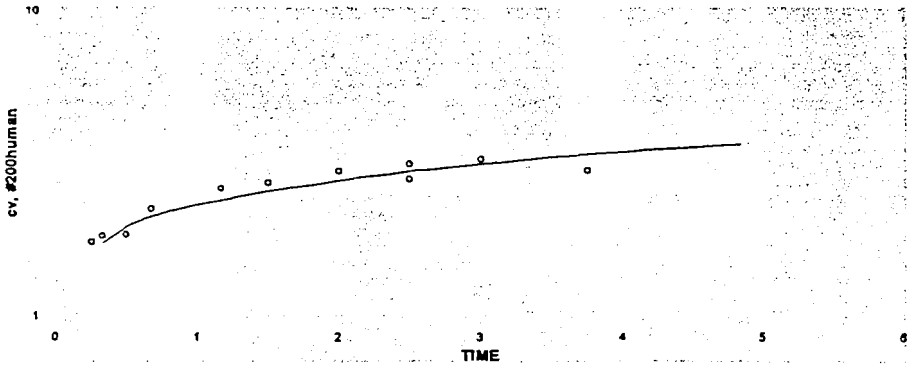


New rat model (with linear metabolism).



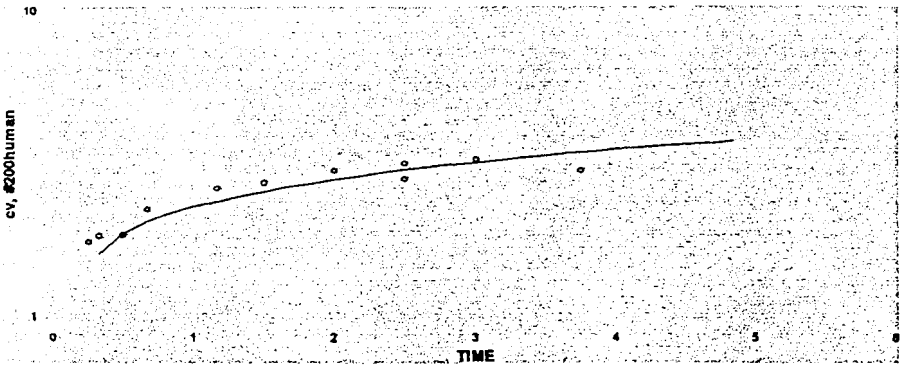
Application of Model to Humans:

200 ppm data sets from multiple papers (human). BW assumed 84.5 kg. The QRC (blood flow to richly perfused) was set at 55% of QC (cardiac output). This model uses Gargas/ Pierce PB (blood: air partition coefficient) of 32 and QFC (blood flow to fat) was then optimized at 10% of QC.



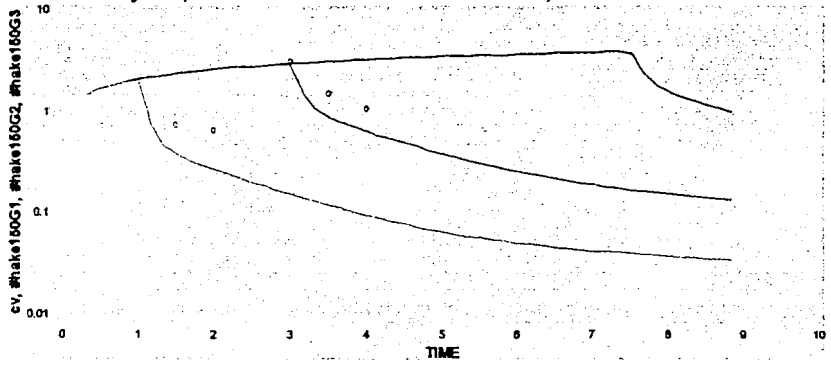
Application of Model to Humans:

If we use Sato's PB (blood: air partition coefficient) of 26.4 instead, we get a better fit with QFC (blood flow to fat) at 8%. The higher PB works better for the early data points.



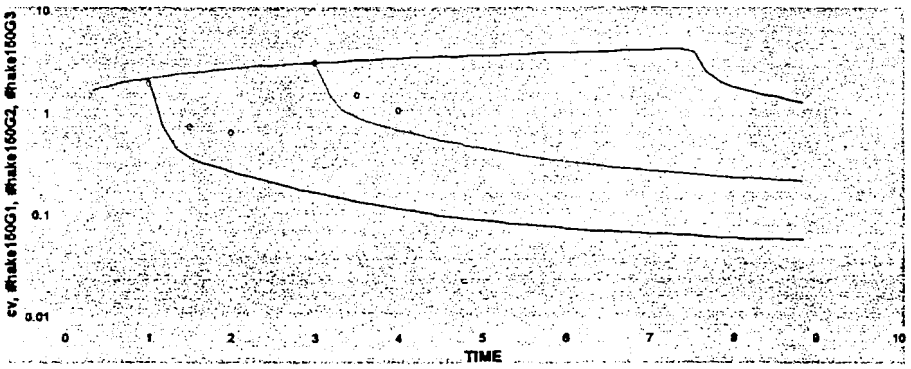
Application of Model to Humans:

Turning to another human dataset (post-exposure blood data by Hake using p-xylene). Measured PBs are 38.5 (Sato/Pierce) and 44.7 (Gargas). If we use the Sato/ Pierce PB, and QFC = .08, best fit the peak blood levels with VmaxC is 5.0 (shown here); if QFC = 0.10, VmaxC appears to be ~ 4 (essentially equivalent to what is shown).



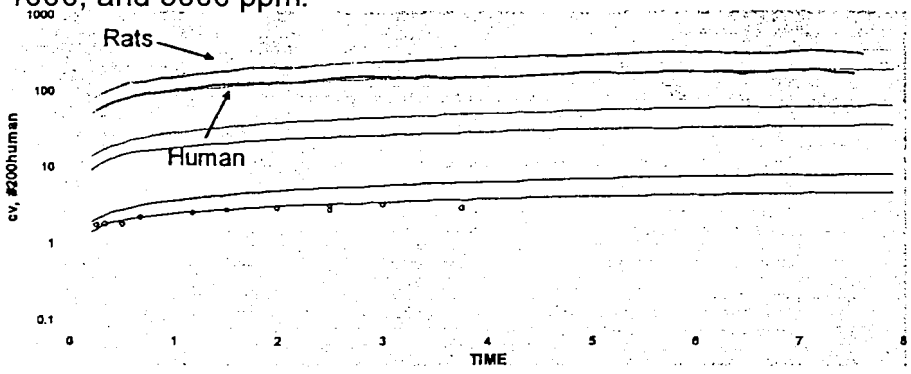
Application of Model to Humans:

Gargas's PB gives essentially same results. Here, PB = 44.7, QFC = 0.1, VmaxC = 4. Thus, while limited data for p-xylene, appears it can be modeled with same parameters as m-xylene except for the expected modification to Vmax. Note: We didn't bother adjusting km too because we don't have data at different exposure levels to work with (practically.)



Comparison of Pharmacokinetics in Rats and Humans:

Rats achieve higher blood concentrations than humans. This is probably mostly due to higher PB measured in rats (46 vs. ~ 26-32 in humans). In this Figure, C_V is plotted for rats and humans using the validated models presented earlier at 200, 1000, and 5000 ppm.



Results of the Model– AEGL-2:

According to this PBPK model, the following exposure concentrations lead to blood concentrations (Cv) equivalent to the rat at 1300 ppm/4 hours (target Cv of 64.2 mg/L)

Duration	low	high	avg	+/-
10 m	7250	9800	8525	15%
30 m	4050	5350	4700	14%
1 h	3280	4150	3715	12%
4 h	2033	2542	2288	11%
8 h	1670	2064	1867	11%

Results of the Model– AEGL-3:

According to this PBPK model, the following exposure concentrations lead to blood concentrations (Cv) equivalent to the rat at 2800 ppm/4 hours (target Cv of 158 mg/L)

Duration	low	high	avg	+/-
10 m	17600	20600	19100	8%
30 m	9850	11200	10525	6%
1 h	7800	9000	8400	7%
4 h	4800	6130	5465	12%
8 h	3970	4975	4473	11%

Effect of work on Cv:

Flow parameters for resting and two work loads:

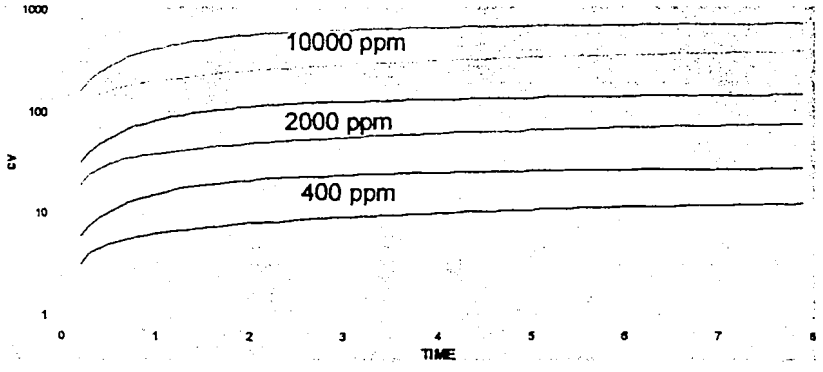
Based on Jonsson (2001): measured QP in five individuals at rest, 50W and 100W;

Johanson (1986): summary of literature values for relative tissue flows to each group at rest, 50W and 100 W.

	QPC	QCC	QLC	QFC	QRC	QSC	Total QFs
Resting, human	18	18	0.26	0.1	0.50	0.14	1.00
50 W, human	53	50	0.13	0.03	0.6	0.24	1.00
100 W, human	87	68.5	0.076	0.03	0.58	0.314	1.00

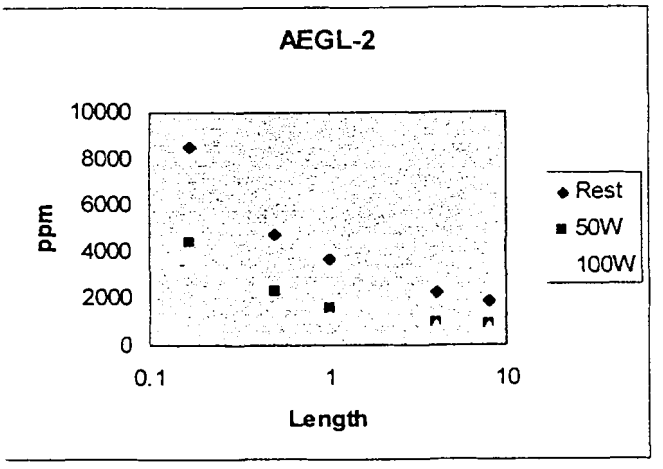
Effect of work on Cv:

Comparison of C_V at rest and at 50W. Curve above each label is 50W and curve below each label is at rest. Model run as before, changing QPC, QCC, and tissue flows per the table on previous slide. Resting conditions based on Gargas parameter set (0.55 QRC, 0.08 QFC, and 32 PB)



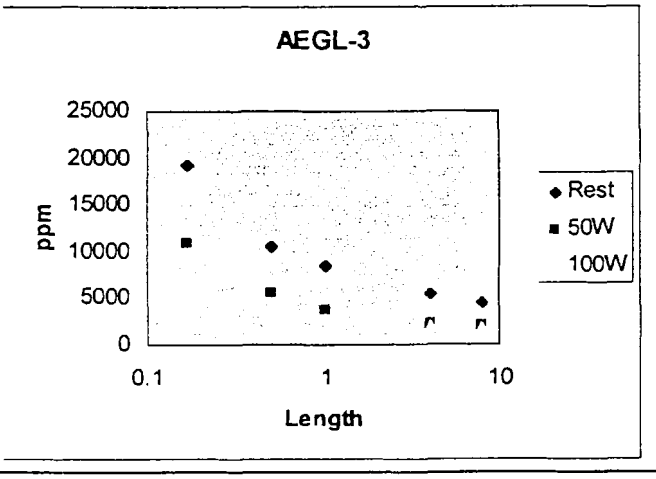
AEGL-2 values computed from the model as specified. Resting values are the average values.

Length	Rest	50W	100W
0.167	8525	4437	3450
0.5	4700	2320	1675
1	3715	1555	1166
4	2288	955	832
8	1867	870	767

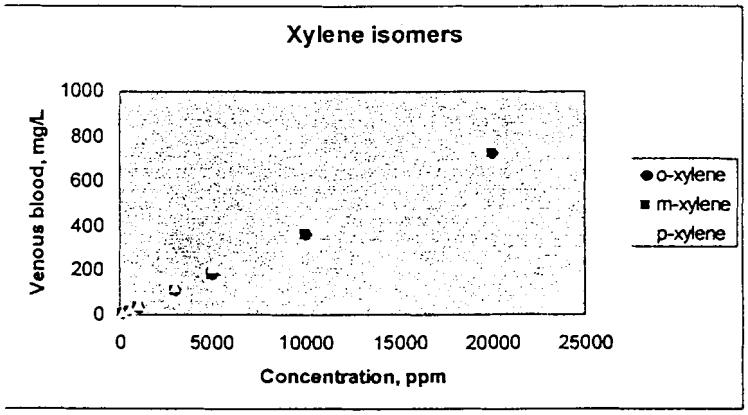


AEGL-3 values computed from the model as specified. Resting values are the average values.

Length	Rest	50W	100W
0.167	19100	10870	8453
0.5	10525	5664	4134
1	8400	3780	2842
4	5465	2305	2121
8	4472.5	2095	1862



Plot comparing the predicted Cv following exposure to individual isomers:



SUMMARY OF AEGL-2 VALUES					
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
NOMEN					
Mean	1165	570	-	-	-
-2 SD	985	483	(430)	(430)	(430)
-3 SD	896	438	-	-	-
PBPK					
Low	7300	4100	3300	2000	1700
Avg	8500	4700	3700	2300	1900
Avg/UF3	2800	1600	1200	760	620
PBPK with 50W work					
Avg	4400	2300	1600	960	870
Avg/UF3	1479	770	520	320	290

SUMMARY OF AEGL-3 VALUES					
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
NOMEN					
Mean	2500	1200	-	-	-
-2 SD	2100	1000	(930)	(930)	(930)
-3 SD	1800	960	-	-	-
PBPK					
Low	17,600	9850	7800	4800	3970
Avg	19,100	10,500	8400	5500	4500
Avg/UF3	6400	3500	2800	1800	1500
PBPK with 50W work					
Avg	10,900	5700	3800	2300	2100
Avg/UF3	3600	1900	1300	770	700

References cited:

Brown, R., Foran, J., Olin, S., and Robinson, D. 1994. Physiological parameter values for PBPK models. A Report Prepared by the International Life Sciences Institute Risk Science Institute.

Carpenter, C.P., Kinkead, E.R., Geary, D.L. Jr., Sullivan, L.J., and King, J.M. 1975b. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. *Toxicol. Appl. Pharmacol.* 33: 543-58.

DeJongh, J., Verhaar, H. J. M., and Hermens, J. L. M. (1998). Role of kinetics in acute lethality of nonreactive volatile organic compounds (VOCs). *Toxicol. Sci.* 45, 26-32.

Gargas, M.L., Burgess, R.J., Voisard, D.E., Cason, G.H., and Anderson, M.E. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98: 87-99.

Haddad S, Tardif R, Charest-Tardif G, Krishnan K. 1999. Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. Toxicol Appl Pharmacol. 161(3):249-57.

References cited (con't):

Hake, C.R.L., Stewart, R.D., Wu, A., et al. 1981. p-Xylene: Development of a biological standard for the industrial worker. Report to the National Institute for Occupational Safety and Health, Cincinnati, OH, by the Medical College of Wisconsin, Inc., Milwaukee, WI. PB82-152844.

Hastings, L., Cooper, G.P., and Burg, W. 1986. Human sensory response to selected petroleum hydrocarbons. In: MacFarland, H.N. ed. Advances in Modern Environmental Toxicology. Vol. VI. Applied Toxicology of Petroleum Hydrocarbons. Princeton, NJ: Princeton Scientific Publishers, pp. 255-270.

Jonsson, F., Bois, F, and Johanson, G. 2001. Phsiologically based pharmacokinetic modeling of inhalation exposure to humans to dichloromethane during moderate exercise. Tox Sci 59:209-218.

Johanson, G. 1986. Physiologically based pharmacokinetic modeling of inhaled 2-butoxyethanol in man. Tox Lett 34:23-31.

Pierce, C.H., Dills, R.L, Silvey, G.W., and Kalman, D.A. 1996. Partition coefficients between human blood or adipose tissue and air for aromatic solvents. Scand. J. Work Environ. Health. 22: 112-118.

References cited (con't):

Sato, A., and Nakajima, T. 1979. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood, and oil. Br. J. Ind. Med. 36: 231-234.

Tardif R, Charest-Tardif G, Brodeur J, Krishnan K. 1997. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicol Appl Pharmacol. 144(1): 120-34.

Tardif R, Lapare S, Krishnan K, Brodeur J. 1993. Physiologically based modeling of the toxicokinetic interaction between toluene and m-xylene in the rat. Toxicol Appl Pharmacol. 120(2):266-73.

Glossary of PBPK Model Terms:

Most used in the presentation:
Cv = venous blood concentration
PB = Blood/air partition coefficient

Physiological parameters

BW = Body weight (kg)
QPC = Alveolar ventilation rate (l/hr/kg)
QCC = Cardiac output (l/hr/kg)
VFC = Fraction fat tissue (kg/(kg/BW))
VLC = Fraction liver tissue (kg/(kg/BW))
VRC = Fraction rapidly perfused (kg/(kg/BW))
QFC = Fractional blood flow to fat ((l/hr)/QC)
QLC = Fractional blood flow to liver ((l/hr)/QC)
QRC= Fractional blood flow to rapidly perfused ((l/hr)/QC)
SF = Scaling coefficent

Chemical-specific parameters

PLA = Liver/air partition coefficient
PFA = Fat/air partition coefficient
PSA = Slowly perfused/air partition coefficient
PRA = Rapidly/air partition coefficient
PB = Blood/air partition coefficient
PL=PLA/PB Liver/blood partition coefficient
PF=PFA/PB Fat/blood partition coefficient
PS=PSA/PB Slowly perfused/blood partition coefficient
PR=PRA/PB Rapidly/blood partition coefficient

MW = Molecular weight (g/mol)
VMAXC = Maximum velocity of metabolism (mg/hr/kg)
KM = Michaelis-Menten (mg/l)
KFC = 0.1
CONC = Inhaled concentration (ppm)

Calculated parameters:

QC = QCC*BW^SF	Cardiac output
QP = QPC*BW^SF	Alveolar vent
VS = VSC*BW	Volume slowly perfused tissue (l)
VF = VFC*BW	Volume fat tissue (l)
VL = VLC*BW	Volume liver (l)
VR= VRC*BW	Volume rapidly perfused (l)
QF = QFC*QC	Blood flow to fat (l/hr)
QL = QLC*QC	Blood flow to liver (l/hr)
QS = QC - QF - QL - QR	Blood flow to non-fat tissue (l/hr)
QR = QRC*QC	Blood flow to rapidly perfused (l/hr)
CIX = CONC*MW/24450	Exposure concentration (mg/l)
VMAX = VMAXC*BW^SF	
KF = KFC/BW^0.3	1st order rate constant for high-capacity/low affinity enzymes

Response to Federal Register Public Comments on Methyl Ethyl Ketone 11/2003

Comments from George V. Alexeeff, Ph.D., D.A.B.T.

Comment:

I would like to raise concerns regarding the AEGL-1 and 2 values recommended by the AEGL Committee for Methyl Ethyl Ketone.

The AEGL-1 is based on human data indicating irritation was objectionable at 350 ppm, and was considered acceptable at 200 ppm following 3-5 minutes of exposure. Another study indicated the absence of objectionable effects after 4 hours of exposure to 200 ppm. The document further discusses the absence of neurobehavioral effects following a 4-hour exposure to 200 ppm. Finally, the document also indicates reports of slight irritation occurred at 100 ppm. Based on these and some supporting studies the document concludes: "therefore, 100 ppm was selected as the threshold for sensory irritation." I suggest the following modifications in this approach that would change the AEGL-1 value slightly, but would be more scientifically defensible:

- Describe the 200 ppm level as the NOAEL for AEGL-1 effects of objectionable irritation and neurobehavioral effects.
- Describe the 350 ppm level as the LOAEL for the AEGL-1 effects of objectionable irritation of the eyes, nose and throat.
- These two changes would be consistent with the standard operating procedures regarding description of the toxicological endpoint of concern.
- If 200 ppm is chosen as the starting point, I suggest that an UF of 3 would be consistent with the committee's previous practice. This would result in an AEGL of 67 ppm, close to the current 100 ppm value. Choice of the 67 ppm value would also address any concerns about the irritation observed in some studies at 100 ppm. Since the endpoint is objectionable irritation, there is no clear justification in the document that there would be no variation in response in the human population.
- The Endpoint described in the Summary Table (page viii, line 6), that is "Threshold for sensory irritation in humans" would be improved if it were revised to "NOAEL for objectionable irritation." Similar changes should occur in the Executive Summary, and summary tables, and derivation section and in the appendix calculations.

Response:

The National Advisory Committee (NAC) for AEGLs passed the values for methyl ethyl ketone (MEK) in December 2001. Values are revisited by the NAC when new data are made available or if there is an obvious misinterpretation of the data. The comments do not address either of these factors.

The 200 ppm level is indeed a NOAEL for AEGL-1 effects of objectionable irritation and neurobehavioral effects. In fact, it is a NOAEL for any effect, and thus is below the definition of the AEGL-1. Newly published studies support 200 ppm as a NOAEL for irritation; these studies have been incorporated into the current TSD. The

recent clinical studies with over 100 healthy male and female subjects and 12 subjects with multiple chemical sensitivity support the use of an intraspecies uncertainty factor of 1. In light of the new data and the previous well-conducted clinical studies of Dick et al. (1984, 1988, 1999, 1992), the AEGL-1 which is presently based on a 1943 study with no analytically-determined concentrations (Nelson et al. 1943) should indeed be revisited.

The editorial comments are appreciated and will be incorporated into the TSD where appropriate. However, we remind the commenter that the phrase, "AEGL values represent *threshold* levels for the general public" appears in the Preface of every TSD.

Comment:

The AEGL 2 rationale is based on the chronic study of Cavendar et al. (1983) in which rats were exposed to 5,000 ppm for 5 days/week for 90 days. The document states: "the 5000 ppm concentration is close to the threshold for neurotoxicity as evidenced by somnolence in another repeated exposure study in which rats were exposed to 6,000 ppm for several weeks (Altenkirch et al. 1978)." If these studies are used as the basis for developing the AEGL-2, I suggest that the document clearly state that:

- The 5000 ppm level is the NOAEL for the AEGL-2 effects of narcosis and that 6000 ppm is the LOAEL for narcosis. The current statement that 5000 ppm is the threshold for narcosis is unclear.

This lack of clarity is exemplified by the statement (page 30, line 6): "Because of the mild endpoint and the nature of the key study and because rodents have a higher respiratory rate and cardiac output than humans, resulting in more rapid uptake of chemical, no interspecies uncertainty factor was applied." The AEGL-2 should not be based on a "mild endpoint." The document must be referring to the AEGL-1 effects that are occurring at the AEGL-2 NOAEL. Because the document did not clearly specify the AEGL-2 NOAEL and LOAEL, as described in the standard operating procedures, the endpoint discussed appears to be unclear. Based on all previous committee discussion, narcosis is not considered a mild endpoint and is considered to be a relevant AEGL-2 effect.

The AEGL-2 does not use an interspecies uncertainty factor, but instead states: "because rodents have a higher respiratory rate and cardiac output than humans, resulting in more rapid uptake of chemical, no interspecies uncertainty factor was applied." No documentation is provided in the document that shows rodents are more sensitive than humans to the AEGL-2 effects. Instead, one of the few human studies addressing this topic, Smith and Mayers (1944) suggests that humans could be more sensitive than rodents since fainting spells were reported at levels close to 600 ppm. Generally pharmacokinetic arguments are justified in reducing an uncertainty factor from 10 to 3. However, since some of the interspecies uncertainty is due to the pharmacodynamics of the response, interspecies uncertainty remains. For the chemical tetrafluoroethane (Volume 2), the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3 was used as supporting documentation. For the chemical 1,1-dichloro-1-fluoroethane (Volume 2), the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3 was also used as supporting

documentation. Thus, previous AEGL values adopted by the committee and the National Research Council appear to support the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3, for a total uncertainty factor of 10. This would reduce the AEGL-2 values to 500 ppm.

I request that the Committee consider these recommendations and revise the AEGL documents accordingly.

Response:

The document will be rewritten to state that 5000 ppm is the NOAEL for narcosis. The term, mild endpoint, will be deleted. It is not clear that 6000 ppm is a LOAEL for narcosis in the rat as the exposures were repeated and the first day on which somnolence was observed was not clearly stated. Furthermore, this effect was "mild" in rodents compared with another chemical tested at the same time. Because rodents have higher respiratory rates and cardiac output (the two primary determinants of systemic uptake of volatile chemicals), than primates, the National Academy of Sciences (NAS) has instructed us to use an uncertainty factor of 1, unless there are data to the contrary. Such data (more rapid uptake and higher blood steady-state concentrations for rodents compared with humans) are available and have been incorporated into the rewritten TSD.

The Smith and Mayers (1944) study is old and has many uncertainties. In addition to inhalation exposures, the workers were dermally exposed as evidenced by "disabling dermatoses." The authors reported that the workers tended to wash their hands in the solvent. The analytical method used to measure atmospheric concentrations in 1944 was not provided. Studies with such shortcomings have been rejected by the NAS as the basis for effects.

Neither tetrafluoroethane nor 1,1-dichloro-1-fluoroethane (NRC 2001, Volume 2) induce narcosis. They are inert gases. It is true that we generally use an intraspecies uncertainty factor of 3 for narcosis. Unfortunately, the use of an interspecies uncertainty factor of 3 was necessary to lower no-effect concentrations for these inert chemicals to levels that would be supportive of the chosen AEGL-1 value. This was not the reasoning for the interspecies uncertainty factor of 1 for the AEGL-2 of MEK. The AEGL-2 was based on a *no-effect level in a subchronic study* with rats (Cavendar 1983).

Comments from John S. Morawetz:

Comments:

I would like to raise concerns regarding the AEGL-2 values recommended by the AEGL Committee for Methyl Ethyl Ketone (MEK).

Need for Interspecies Uncertainty Factor

The current AEGL 2 rationale is based on the chronic study of Cavendar, 1983 in which rats were exposed to 5,000 ppm for 90 days. The committee did not use any interspecies uncertainty factor because this was a no-effect repeated-exposure study but the rats in the Altenkirch, 6,000 ppm study, developed somnolence within 5 to 10 minutes. In addition, the TSD notes that this study was begun at 10,000 ppm but lowered to 6,000 within a few days due to "severe irritation of the respiratory tract".

Alternatively, the 5,000 ppm Cavendar exposure should be considered a 10 minute threshold for AEGL-2 due to both rapid somnolence (a surrogate for difficulty to escape) and severe enough respiratory irritation at higher exposures to force lower study exposures. If the repeated exposure is then not present, an interspecies uncertainty factor of 3 should be applied for AEGL-2 values while starting with the 5,000 ppm exposure. With the intraspecies uncertainty factor of 3 the resulting levels would be supported by Smith and Mayers which found two cases of fainting at exposures of up to 600 ppm (likely area samples of unknown duration). This study also found significant numbness in the legs and "a tendency for them to suddenly give way under him", symptoms which might cause difficulty in escape.

Response:
See previous answer concerning use of an interspecies uncertainty factor of 1. In addition, the Smith and Mayers (1944) study is poor support for a value of 500 ppm for the reasons cited above (dermal uptake, repeated exposures , analytical methodology not specified) as well as the fact that (as John states) these were probably area samples of unknown duration. Furthermore, the numbness in the legs is a result of chronic exposure, not a single exposure.

Comments from Mary Lee Hultin
Toxicology Specialist
Air Quality Division
Michigan Department of Environmental Quality

Comment:
AEGL-1 value:
While selection of 100 ppm as the threshold for sensory irritation appears to be the prudent and conservative choice for derivation of the AEGL-1, questions still remain as to the most germane principal study and the use of uncertainty factors. According to the documentation provided with the California Acute Reference Exposure Level (REL) dated March 1999, the Dick et al. (1992) and Nelson et al. (1943) studies are contradictory. The former identified a 4-hour NOAEL for irritation and neurobehavioral effects of 200 ppm while the latter reported a 3-minute LOAEL of 200 ppm for irritation.
The California REL for methyl ethyl ketone (MEK) uses the study of Nakaaki (1974), which reports a LOAEL of 270 ppm for "subjective reports of eye, nose, and throat irritation, lacrimation, and sneezing." An uncertainty factor (UF) of 6 was applied to this LOAEL, as was

an interspecies UF of 1 and intraspecies UF of 10 (total UF of 60). Overall, the current CA REL for MEK is 4.5 ppm, or 13 mg/m3. Furthermore, the AEGL-1 based on work of Nelson et al. (1943), which has been characterized as having less accurate MEK measurements and less sophisticated evaluation of irritation than later studies (specifically, Dick et al. 1992 and Nakaaki 1974). Personal communications between CA REL staff and Dick indicates that study should be thrown out as it was not designed to measure irritation thresholds. The Nakaaki (1974) study is not without uncertainty, as the nature of this study (which slowly increased MEK concentrations over a 2-hr period) complicates effort to identify a NOAEL/LOAEL for irritation effects. If it is assumed that the threshold is 100 ppm (from the Nelson study); there should be an intraspecies UF of 10 applied to the selected AEGL-1 threshold value, yielding a new value of 10 ppm. This reviewer suggests using this value of 10 ppm for the 10-, 30-, and 60-minute AEGLs. This would be more in line with risk assessment values from CA, where staff identified a level protective against "severe" adverse effects for a 7-hour exposure to MEK of 11 ppm. This value is nearly an order of magnitude lower than the "mild" effects AEGL-1 value

Response:
The NAC did not find the Dick et al. (1992) and Nelson et al. (1943) studies entirely contradictory. The Dick et al. authors did not find symptoms of irritation at 200 ppm and the Nelson et al. (1943) subjects were willing to tolerate 200 ppm for 8 hours.

As noted, it is important to assess the quality of papers. The Nelson et al. (1943) paper is 60 years old. The exposures were for 3 to 5 minutes. There were no analytical measurements. The study does not meet current standards. It is interesting to note that the paper does state that, "the majority of subjects considered 200 ppm satisfactory for an 8-hour exposure." Where is the "severe" irritation that is being guarded against?
The Nakaaki (1974) paper addressed neurobehavioral effects, and reports of irritation were incidental to the subject of the paper. Even the neurobehavioral study was not a standard one and the paper is dated compared to recent well-conducted studies. As the commenter notes, the exposures in the Nakaaki paper were not constant, but increased over time. Different neurobehavioral results were reported for several other solvents tested in the study (neurobehavioral changes are similar for most solvents). Sensory symptoms are noted, but specific sensory symptoms were not related to specific concentration. But, more troubling is the fact that these symptoms of sensory irritation are NOT REPORTED IN ANY OTHER PAPER... when exposures were to similar concentrations. Therefore, these results must be viewed as questionable.

The Dick et al. studies (1984, 1988, 1992) are well conducted and used adequate numbers of subjects. To disregard the Dick studies because they do not address the threshold for irritation is ludicrous (the Nakaaki 1974 paper also did not address the threshold for sensory irritation). The Dick et al. studies do address subjective symptoms and add to the weight of evidence that 200 ppm is not an irritating concentration. However, additional recent papers that have been added to the MEK TSD may be more suitable as the key

study for the AEGL-1 (see revised TSD).

Toxicologists who do risk assessments should be familiar with the physical and chemical properties of chemicals as well as the mechanism of action. Solvents are not irritants until concentrations of several thousand ppm are reached. Evidence for this is seen in the mouse RD_{50} tests in which concentrations of 9000 to 30,000 were measured or projected as the RD_{50}. MEK has a strong, but not necessarily unpleasant, odor. Odor does not constitute a material health impairment. The concentration of 4.5 ppm (or 10 ppm) would not be defensible for emergency situations in light of the current studies which show no irritation at 200 ppm. Even individuals with self-reported multiple chemical sensitivity did not find concentrations that ranged up to 380 ppm irritating (Seeber et al. 2002). These individuals reported no irritation when tested at 10 ppm.

It should be noted that the AEGL-1 value is lower than many workplace standards which are protective of irritation under repeated or chronic work conditions. The AEGL-1 of 100 ppm is below the 200 ppm of the ACGIH TLV-TWA , OSHA and NIOSH PELs, and German and Dutch workplace standards. The commenter is suggesting that a value that is 1/20th of these standards should be used *under emergency conditions*. Is the commenter suggesting that the California acute RfD should take precedence over the long-established workplace guidelines for chronic exposures?

Comment:
AEGL-2 value:
It is unclear to this reviewer why neurological endpoints were used when it appears fairly clear that the most sensitive endpoint for MEK toxicity is developmental (specifically, the mild fetotoxicity seen from the experiments of Schwetz, Deacon and Mast). Schwetz et al. (1974) identified a LOAEL for lowered birth rats - pregnant rats exposed to 1,000 ppm MEK for 7 hrs/day on days 6-15 of gestation showed statistically significant lower birth weight, shorter rump length, and greater incidence of skeletal abnormalities among pups. This experiment was repeated by Deacon et al. (1981), who added another exposure category, and the results indicated a reproductive LOAEL among rats of 3,000 ppm. Later, Schwetz et al. (1991) repeated the same study using mice instead of rats and these results indicated reproductive LOAEL in mice of 3,000 ppm. The totality of this evidence points indicates that the LOAEL for reproductive effects is likely 3,000 ppm among murine test animals.
Based on these same reproductive toxicity studies, CA REL staff identified a level protective against severe adverse effects for a 7-hour exposure to MEK: 11 ppm (which is 2 full orders of magnitude lower than the proposed AEGL-2 of 1700 ppm. According to HSDB, workers exposed to 300-500 ppm complained of headache, irritation and nausea. Furthermore, two other occupational exposures that involved exposure to MEK in the range of 398 to 561 ppm and acetone in the range of 330 to 495 ppm complained of stomach distress, watery eyes, and headache while conscious; both employees either fainted or were found unconscious following exposure. Unless there is a significant synergism with acetone (such as seen with concurrent

exposures to MEK and n-hexane), this "disabling" (i.e. unconsciousness) effect of MEK inhalation exposure is considerably less than the proposed 1700 ppm AEGL-2. In fact, having unconsciousness (in essence, an impaired ability to escape) result from exposures of "only" 400-600 ppm seems to strengthen the argument to use an intraspecies uncertainty factor of 10 to account for individual variation in response.

Principal studies used by EPA to set the RfC are those done by Schwetz et al. (1991) and Mast et al. (1989); these are considered "one single study," according to EPA's IRIS database. These studies identified a LOAEL of 3020 ppm and NOAEL of 1126 ppm, based on an endpoint of mild, but significant, developmental toxicity in exposed pregnant mice. In addition, they had "medium confidence" in this principal study and thus, assigned uncertainty factors of 10 for interspecies extrapolation, intraspecies sensitivity, and incomplete database (lack of chronic and reproductive toxicity studies). An additional modifying factor of 3 was applied for lack of data on respiratory tract effects for a total uncertainty factor of 3000.

This reviewer suggests the use of the LOAEL identified for developmental endpoints along with uncertainty factors of 10 for both intraspecies and interspecies extrapolation. Furthermore, this reviewer suggests using a modifying factor of 3 to account for database insufficiency and uncertainty involved with applying these developmental effects studies to exposures of 10-, 30-, or 60-minutes. This would yield an AEGL-2 value of 100 ppm.

Response:

MEK is clearly not a developmental toxicant. The fetal effects found in the Schwetz et al. (1974) study could not be repeated in the Deacon et al. (1981) study. The slight fetotoxicity observed among litters of rats exposed to 3000 ppm in the Deacon et al. study involved only an increased incidence of minor skeletal variants. These effects such as extra ribs disappear after birth. And, these effects were accompanied by maternal toxicity in the Deacon et al. study. Considering the higher respiratory rate and higher uptake in rats, and considering that rats were exposed for half of their gestation period (10 of 20 days) and the effects were minor and reversible, the suggestion that this might occur during a 0.3% time period in the human gestation period (an 8-hour period in a 270-day human pregnancy) did not seem likely. It is unlikely that an 8-hour exposure would result in a reduced weight gain in humans over the 270-day period.... the sign of maternal toxicity in rats. Therefore, the NAC chose not to use the developmental studies as the AEGL-2 endpoint. Nevertheless, the chosen AEGL-2 value of 1700 ppm is clearly below the repeat 3000 ppm value that was responsible for the observed effect in rats.

The NAC does not disagree with the U.S. EPA concerning the LOAEL and NOAEL in the Schwetz and Mast studies. However, the effects were minor. In addition, the U.S. EPA sets a Reference Dose, i.e., a lifetime exposure for MEK. The NAC sets a one-time, ≤8-hour exposure for emergency conditions. Concerning uncertainty and modifying factors, it has been the consensus of the NAC and their primary reviewer, the National Academy of Sciences, that uncertainty and modifying factors for AEGLs need not be as stringent as for lifetime exposures.

The studies cited by the commenter (HSDB; Smith and Mayers 1944), as noted above, suffer from many shortcomings. They do not hold up in light of recent, well-conducted studies with careful analytical measurements and surveys of symptoms. These recent studies involve exposures of over 100 healthy individuals as well as a dozen individuals with self-reported multiple chemical sensitivity, a group particularly sensitive to solvent exposure (see Table 2 of revised TSD).

Comment:
AEGL-3 value:
Regarding the AEGL-3, both the AEGL draft document and CA REL staff considered the La Belle and Briger (1955) study as the only one pertinent for development of a life-threatening exposure limit; however, there are differences in methodology for further analysis of this data. The AEGL draft document mentions a study by Hansen et al (1992) – which the CA REL staff do not consider – in which there were no deaths in mice exposed to the maximal study concentration of 26,416 ppm for 30 minutes. In contrast, a CA REL document (but not the AEGL draft document) mentions two later statistical studies done on the 1955 data by Kenneth Crump (Crump and Howe, 1983; Crump, 1984), where the BC05, adjusted for one-hour exposure, was determined to be 14,124 ppm. (The BC01 was also found to be 5790 ppm by Crump's retrospective analysis of the 1955 data.) Fowles et al. (1999) also did some later statistical recrunching of the 1955 data (which was mentioned in AEGL draft document but not the CA REL document) and came up with a MLE01 of 7500 ppm. If one compares lethality data from mice and rats, it appears as if concentrations of roughly 8000 ppm will not cause lethality in mice exposed for 4 hours but will cause 50% lethality in rats exposed for 8 hours.
The NIOSH IDLH is set at 3000 ppm; this level is presumably valid for up to 30-minute exposures. This is considerably less than 30-min "lethal" AEGL-3 of 10,000 ppm.
There appears to be sufficient variation in response between animals with regard to the lethality data to argue for using uncertainty factors of 10 for interspecies and extrapolation for all exposure periods (10-minute through 8-hour). This would yield an AEGL-3 value of 1000 ppm for the 10- and 30-minute exposures. The other AEGL-3 values should be recalculated using an assumed interspecies UF of 10 and not 3.

Response:
It has been the experience of the NAC that mice are generally more sensitive to chemical exposure than rats.... presumably due to their small size and higher respiratory rate. That said, the difference in the lethality for these two species in the two cited studies (Pozanni 1959 and LaBelle and Brieger 1955), both quite old, is not a factor of 10; it is at the most, a factor of 2 if either value is time scaled to the other time. The LaBelle and Brieger study is dated, and if more recent studies with longer exposure durations had been available, they might have been used. The 30-minute study of Hansen et al. (1992) is appropriate for the shorter AEGL-3 exposure durations, not only because it is recent and well-conducted, but also because pharmacokinetic data indicate that uptake would not reach steady state during the 30-minute exposure. Tracheally-cannulated mice also survived the exposures

and there was no serious depression of the central nervous system. The study of Zakhari (1977; no deaths at 50,000 ppm for 45 minutes) supports the Hansen et al. (1992) study.

Comments from S.P. Glenn
Clean Channel Association
Pasadena, Texas

Comment:
I am concerned with some of the AEGL values recommended by the AEGL Committee as they approach the Lower Explosive Level (LEL). The emergency response community has used 10% LEL as their action levels for many years. This safety margin takes into account the error of the instruments and the conditions under which these measurements are taken. The Incident Commander is reminded to re-evaluate any response actions that entry team members would take when levels are above the action level; using higher levels may place teams in dangerous environments without considering other options.

I request the committee remove any value from the summary tables that are above 50% of the LEL. This will prevent emergency responders from erroneously assuming that these levels would not have potential lethal results. When derived values are above 50% of the LEL, the recommended numbers should not be within the summary tables but instead put in a footnote. Levels above 10% of the LEL can be within the tables with a footnote similar to that used for some of the published chemicals.

Both Methyl Ethyl Ketone (MEK) and Xylene have this situation. MEK's 10 and 30-minute values are half the 18,000 ppm LEL. I request the committee put these values in a note below the table. The AEGL-3 values for 1 hour (4,000 ppm) and 4 and 8 hours (both 2,500 ppm) are above 10% of the LEL for MEK. I request that committee mention this in a footnote in the summary tables.

For Xylene, the 10-minute AEGL-3 value of 2,100 ppm is above 10% of the LEL for all forms of Xylene (oxylene (9,000 ppm) and m-and p-xylene LEL (11,000 ppm)) and should be noted in all summary tables. Since the other AEGL 3 values are between 10% of the LEL for o-xylene and m-and p-xylene (11,000 ppm) an additional note should be added to enable emergency responders to draw their own conclusions.

Response:
The original TSD on methyl ethyl ketone was written several years ago. Since that time, the NAC approved adding notations to the Summary Table when the 10 or 50% LEL for a chemical is exceeded. Notations concerning exceedence of the 10 and 50% LEL have been added to the AEGL-3 values in the Summary Table of the revised document.

Reconsideration of
ACUTE EXPOSURE GUIDELINE LEVELS
for
METHYL ETHYL KETONE

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bill Bress

Chemical Reviewer:
Loren Koller

METHYL ETHYL KETONE

Reconsideration of AEGL-1

Present AEGL-1 is 100 ppm
- based on Nelson et al. (1943) study of 3-5 minutes duration with no analytical measurements + Dick et al. 1992

Consider raising AEGL-1 to 200 ppm
- Solvents are not irritants

Recent, well-conducted studies:
- Dick et al. (1992) ... 24 subjects
  - 200 ppm for 4 hours
    - odor unobjectionable
    - no subjective symptoms
- Shibata et al. (2002)... 4 subjects, with exercise
  - 200 ppm for 2 hours
    - noticeable odor
    - no irritation, no subjective symptoms

- Muttray et al. (2002)... 19 subjects
  - 200 ppm for 4 hours
    - strong odor
    - no irritation
- Seeber et al. (2002)... 24 subjects (12 MCSs)
  - 10-380 ppm for 4 hours
  - (five 8-minute peaks to 380 ppm)
  - odor was clearly distinguished from irritation
    - intense odor
    - irritation rated "not at all" - healthy subjects
      - "hardly at all" MCS subjects
- Metabolism studies with routine exposures to 200, 300, or 400 ppm, some with exercise

METHYL ETHYL KETONE

Re-wording of AEGL-3 for 10 and 30 minutes

Based on ***projected*** 30-minute mouse RD_{50} of 31,426 ppm (Hansen et al. 1992)
- This concentration was ***not*** actually tested
- The highest tested concentration was 26,416 ppm - no deaths

Supported by rat 30-minute non-lethal concentration of 92,239 ppm (Klimisch 1988)

Suggestion: Keep the 10- and 30-minute AEGL-3 values at 10,000 ppm. Use the Klimisch 1988 study as the basis, with inter- and intraspecies uncertainty factors of 3 and 3, respectively. Use the Hansen et al 1992 study (26,416 ppm) as support with inter- and intraspecies uncertainty factors of 1 (mouse more sensitive) and 3, respectively. Also supported by no deaths in mice exposed to 50,000 ppm for 45 minutes (Zakhari 1977).

METHYL ETHYL KETONE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	*200 ppm*	*200 ppm*	*200 ppm*	*200 ppm*	*200 ppm*
AEGL-2	1700 ppm	1700 ppm	1700 ppm	1700 ppm	1700 ppm
AEGL-3*	10,000 ppm	10,000 ppm	4000 ppm	2500 ppm	2500 ppm

* All AEGL-3 values footnoted for explosive limits.

METHYL ETHYL KETONE AEGLs

Suggestion for AEGL-2:
Flatline the present AEGL-2 value at 1, 4 and 8 hours only (no data for 1-hour value).

At low concentrations of 200 and 400 ppm, MEK approaches steady-state in the blood of human subjects by 3 hours (Liira et al. 1990a). At higher concentrations, steady state takes longer. The data show that higher exposures can be tolerated at the shorter time periods for a common endpoint. The AEGL-2 was based on the threshold for narcosis in a subchronic study with the rat.... 5000 ppm, 6 hours/day, for 90 days (Cavender et al. 1983).

For example, a concentration of 10,000 ppm for 30 minutes did not induce narcosis in the mouse, a more sensitive species than the rat (Hansen et al. 1992). At 10,000 ppm, rats were more active than controls during the first 10 minutes of exposure (Altenkirch et al. 1978a). The concentration of 10,000 ppm is strongly irritating to humans (Patty et al. 1935), but dividing the 10,000 ppm concentration by an intraspecies uncertainty factor of 3 results in 3300 ppm, a concentration with only moderate irritation, and thus within the definition of the AEGL-2.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	3300 ppm	3300 ppm	1700 ppm	1700 ppm	1700 ppm

OR: time scale back from the 4-hour exposure using the default value of n = 3.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	4900 ppm	3400 ppm	2700 ppm	1700 ppm	1700 ppm

METHYL ETHYL KETONE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm
AEGL-2	4900 ppm	3400 ppm	2700 ppm	1700 ppm	1700 ppm
AEGL-3*	10,000 ppm	10,000 ppm	4000 ppm	2500 ppm	2500 ppm

* All AEGL-3 values footnoted for explosive limits.

The AEGL-2 values for 10 and 30 minutes and 1 hour would be footnoted as exceeding 1/10th of the LEL (LEL = 18,000 ppm).

December 10, 2003

ACRYLIC ACID AEGL-2 REVISIT AND DIRECTIONS FOR NAS-13 MEETING IN JANUARY 28, 2004.

HISTORY OF ACRYLIC ACID AEGL-2

FR PUBLICATION MAY 5, 2001 (**30-30-20-9.4-6.4**)
- POD
  - rat
  - 6 hrs
  - 75 ppm
  - Total UF = 10

INTERIM AT NAC-24 ON APRIL 9, 2002 (BALLOT **68-68-46-21-14**)
- POD
  - monkey/rat
  - 3 hrs
  - 75 ppm
  - Total UF = 3

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

PRESENTED TO NAS-11 ON JANUARY 27, 2003 (**100-100-68-31-21**)
- POD
  - monkey/rat
  - 6 hrs
  - 75 ppm
  - Total UF = 3

DISCUSSED AT NAC-30 ON SEPTEMBER 16, 2003 IN RESPONSE TO NAS-11 COMMENTS (**100-100-68-31-21**)
- POD
  - monkey/rat
  - 6 hrs
  - 75 ppm
  - Total UF = 3

KEY STUDIES DISCUSSED FOR THE AEGL-2

MONKEYS (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997)

Single exposure to 75 ppm for 3 and 6 hours

3 hour exposure = 20 % of olfactory epithelium had acrylic acid induced damage
6 hour exposure = 40-60% of olfactory epithelium had acrylic acid induced damage

Nasal lesions were restricted to the olfactory epithelium lining the dorsal medial meatus at the level of the maxillary sinus in the proximal aspect of both nasal passages. The morphologic alterations consistently found in all acrylic acid-exposed monkeys were focal degeneration and necrosis of the olfactory epithelium with mild inflammation (influx of neutrophils and lymphocytes)

The extent and severity of the lesions were slightly greater in monkeys exposed for 6 hours compared to those exposed for 3 hours. The severity of epithelial injury ranged from mild apical blebbing and cytoplasmic vacuolation of the olfactory sustentacular cells to marked necrosis, exfoliation and attenuation of the olfactory epithelium with only a few remaining basal or sensory cells attached to the basement membrane.

Approximately 20 % and 40-60 % of the olfactory epithelium in the examined sections had acrylic acid induced damage after 3 or 6 hours, respectively. The author concluded that monkeys exposed to acrylic acid had focal, olfactory epithelial lesions that resembled in both nature and severity those reported in rodents.

RATS (Frederick et al., 1998)

Single exposure to 75 ppm for 3 and 6 hours
Harkema (2001) concluded that monkeys exposed to acrylic acid had focal, olfactory epithelial lesions that resembled in both nature and severity those reported in rodents.

WHY WAS 3 HOURS CHOSEN FOR THE POD RATHER THAN 6 HOURS IN NAC-24?

The 3 hour duration was suggested as a middle way. There was no formal discussion of 3 vs 6 hours. There was discussion of uncertainties about which animals were experimental and which were control. Especially in light of some respiratory difficulty seen in one animal. This uncertainty was cited as further support for using 3 vs 6 hours for the POD. However, closer inspection of the Rohm and Haas study indicates that the monkey experiencing respiratory difficulty was in the ethyl acrylate exposed group, not the acrylic acid exposed group.

WHY WAS 68 PPM CHOSEN FOR BOTH THE 30 AND 10 MINUTE VALUES WHEN THE 3 HOUR STUDY WAS USED FOR THE POD IN NAC-24?

Since 75 ppm was the highest dose in monkeys for which data existed, and since rabbits experienced blepharospasm at 129 ppm but not at 77 ppm, the committee was uncomfortable allowing exposures over 75 ppm. For that reason, the 68 ppm value for the 30 minute duration was used for the 10 minute exposure.

Multiple exposure developmental toxicity studies with results observed during first exposure

Species	ppm	Duration	Effect	Reference
rabbit	129	6 hr	blepharospasm	Neeper-Bradley et al., 1997
rabbit	77	6 hr	no blepharospasm	
rat	439	6 hr	eyelid closure & considerable discharge from eyes and nose	Klimisch and Hellwig, 1991
rat	218	6 hr	eyelid closure & discharge from eyes, slightly reddened nose	
rat	114	6 hr	no signs of irritation	
mouse	223		scratching at the nose as a sign of irritation	Miller et al. (1980)
mouse	75		no signs of irritation	

VERBIAGE FROM THE NAC-24 MINUTES

With regard to AEGL-2, the AEGL Development Team considered a level of 75 ppm as an adequate threshold for an AEGL-2 effect because at higher concentrations, clinical effects occurred in animals (tearing and blepharospasm) that could impair the ability to escape, and because olfactory tissue destruction which increases with the exposure concentration is increasingly likely to result in permanent damage of the olfactory epithelium. The available animal data clearly demonstrate that the degree of olfactory epithelium damage increases with increasing exposure time and, thus, argue against using the same exposure concentration as the AEGL-2 value for all relevant periods of time. The AEGL Development Team suggested incorporation of the monkey study into the TSD. This study, together with the histopathological analysis was considered an adequate basis for a further reduction of the interspecies factor to 1. At the same time, this study strengthens the rationale for reduction of the default interspecies factor. For the AEGL-2 derivation, the monkey study will be used as an additional key study. The motion to accept the revised AEGL-2 values was made by Bob Snyder and seconded by Steve Barbee. The motion passed (YES:17; NO:4; Abstain:0) (Appendix F).

SYNOPSIS OF NAS COMMENTS ON AEGL-2 VALUES

1. The Subcommittee is not convinced that histological changes in the olfactory epithelium is the most appropriate endpoint for AEGL-2.

2. The AEGL seems conservative given the relatively subtle changes. COT raises the question whether the olfactory epithelium has the capacity to repair/regenerate.

OPTIONS

1. PRESENT THE ORIGINALLY BALLOTED VALUES TO THE NAS (**68-68-46-21-14**)

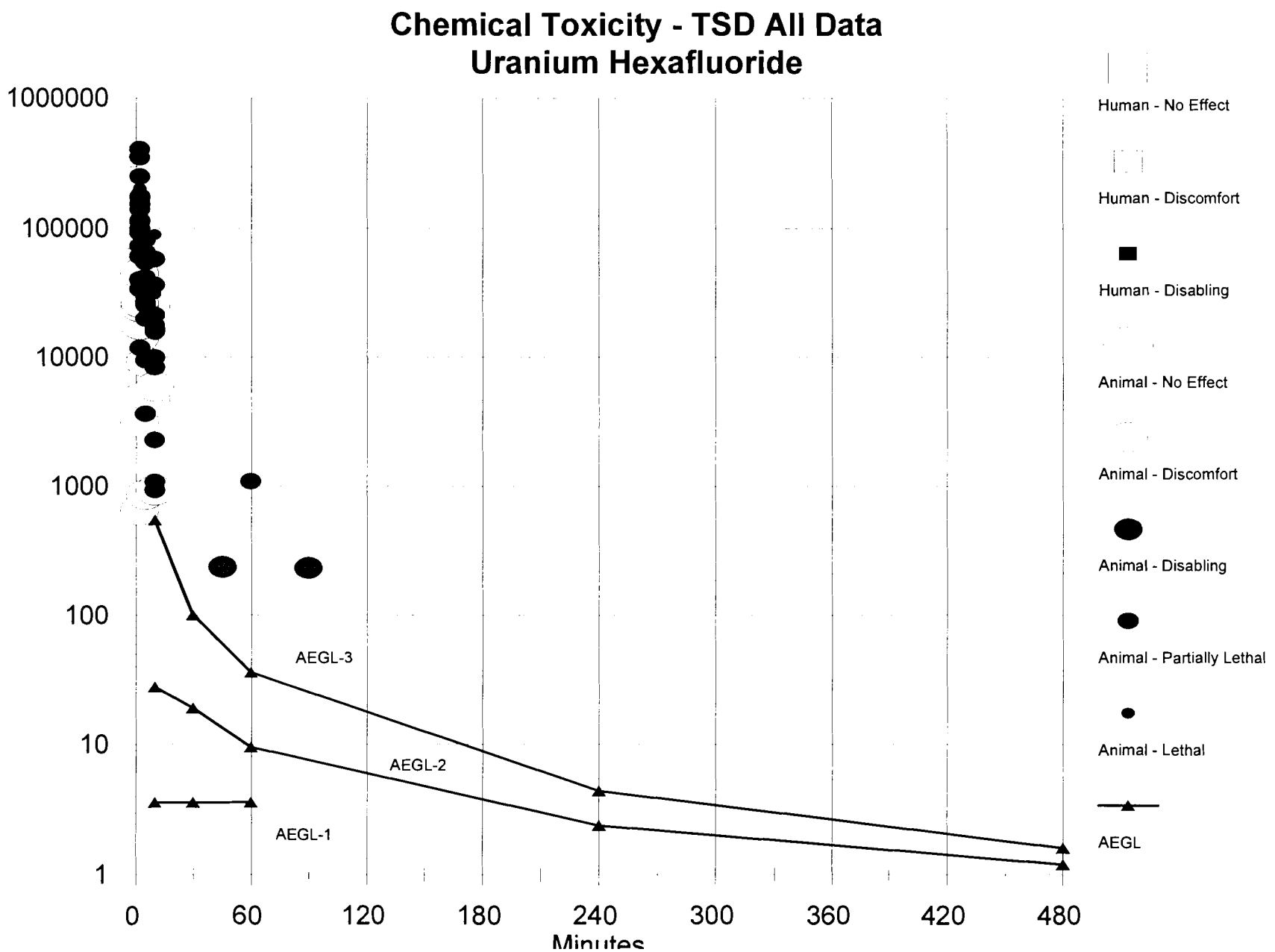
   Not consistent with SOP direction on choice of POD effect. The highest exposure not causeing irreversible effects is 6 hours, not 3 hours.

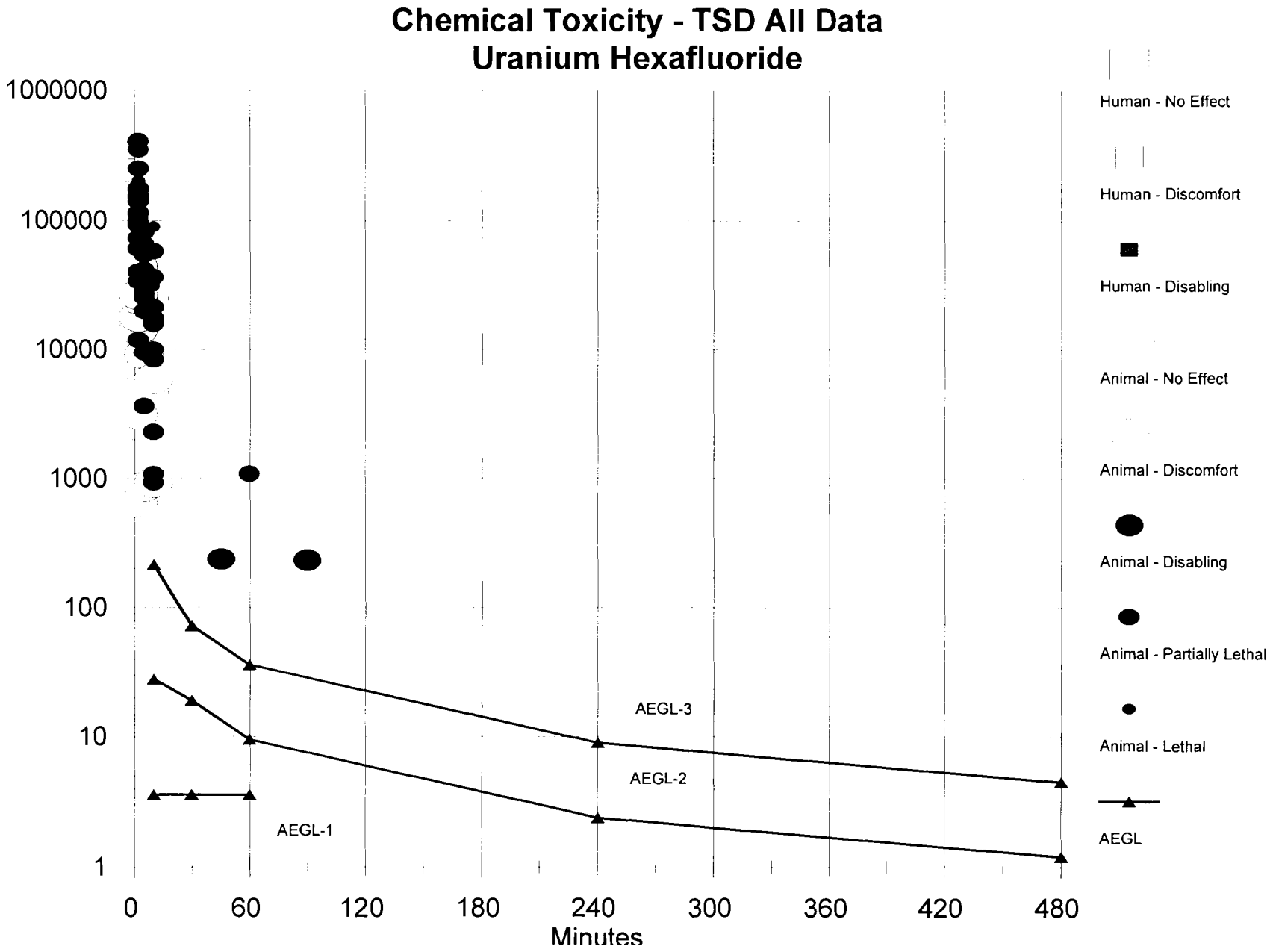
2. RE-BALLOT THE AEGL-2 VALUES TO (**100-100-68-31-21**)

   AEGL-2 values for 10 minutes and 30 minutes exceed the 77 ppm level which did not cause blepharospasm in rabbits. The no effect level for eyelid closure & discharge from eyes in rats is 114 ppm.

3. OTHER?

ATTACHMENT 12




Chemical Toxicity - TSD All Data
Uranium Hexafluoride
1000000
100000
10000
1000
100
10
1
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

Comparison of AEGL Values for Uranium Hexafluoride and Hydrogen Fluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
UF_6 AEGL-1	**0.25 ppm UF_6 3.6 mg/m^3** **1.0 ppm HF 0.8 mg/m^3**	**0.25 ppm UF_6 3.6 mg/m^3** **1.0 ppm HF 0.8 mg/m^3**	**0.25 ppm UF_6 3.6 mg/m^3** **1.0 ppm HF 0.8 mg/m^3**	**NR**	**NR**	**Modification of HF AEGL-1 values**
HF AEGL-1	**1.0 ppm 0.8 mg/m^3**	**1.0 ppm 0.8 mg/m^3**	**1.0 ppm 0.8 mg/m^3**	**1.0 ppm 0.8 mg/m^3**	**1.0 ppm 0.8 mg/m^3**	**Pulmonary irritation threshold in humans**
UF_6 AEGL-2	**1.9 ppm UF_6 28 mg/m^3** **7.8 ppm HF 6.4 mg/m^3**	**1.3 ppm UF_6 19 mg/m^3** **5.3 ppm HF 4.3 mg/m^3**	**0.67 ppm UF_6 9.6 mg/m^3** **2.7 ppm HF 2.2 mg/m^3**	**0.17 ppm UF_6 2.4 mg/m^3** **0.67 ppm HF 0.55 mg/m^3**	**0.083 ppm UF_6 1.2 mg/m^3** **0.33 ppm HF 0.27 mg/m^3**	**Renal pathology in dogs**
HF AEGL-2	**95 ppm 78 mg/m^3**	**34 ppm 28 mg/m^3**	**24 ppm 20 mg/m^3**	**12 ppm 9.8 mg/m^3**	**8.6 ppm 7.0 mg/m^3**	**NOAEL for lung effects in rats; sensory irritation in dogs**

Comparison of AEGL Values for Uranium Hexafluoride and Hydrogen Fluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
CURRENT UF_6 AEGL-3	**38 ppm UF_6** **550 mg/m^3** 150 ppm HF 123 mg/m^3	**7.3 ppm UF_6** **100 mg/m^3** 29 ppm HF 24 mg/m^3	**2.5 ppm UF_6** **36 mg/m^3** 10 ppm HF 8.2 mg/m^3	**0.31 ppm UF_6** **4.4 mg/m^3** 1.2 ppm HF 0.98 mg/m^3	**0.11 ppm UF_6** **1.6 mg/m^3** 0.44 ppm HF 0.36 mg/m^3	**Lethality threshold in rats**
PROPOSED UF_6 AEGL-3	**15 ppm UF_6** **216 mg/m^3** 60 ppm HF 49 mg/m^3	**5.0 ppm UF_6** **72 mg/m^3** 20 ppm HF 16 mg/m^3	**2.5 ppm UF_6** **36 mg/m^3** 10 ppm HF 8.2 mg/m^3	**0.63 ppm UF_6** **9.0 mg/m^3** 2.5 ppm HF 2.1 mg/m^3	**0.32 ppm UF_6** **4.5 mg/m^3** 1.3 ppm HF 1.1 mg/m^3	**Lethality threshold in rats**
HF AEGL-3	170 ppm 139 mg/m^3	62 ppm 51 mg/m^3	44 ppm 36 mg/m^3	22 ppm 18 mg/m^3	15 ppm 12 mg/m^3	**Lethality threshold in rats**

ACUTE EXPOSURE GUIDELINE LEVELS
for
HYDROGEN IODIDE

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Mark McClanahan (Ernie Falke)

Chemical Reviewers:
Nancy Kim
Richard Niemeier

HYDROGEN IODIDE

There are no data from which to derive AEGL values for HI

Two options:
1. Do not derive values
2. Use the values derived for the most chemically similar hydrogen halide, HBr (MW: F = 19; Cl = 35.5; Br = 80; I = 127).

Structure-Activity Relationships
- Extensive data for HF and HCl; minimal data for HBr
- For the endpoint of lethality, toxicity is HF>HBr>HCL
- For the endpoint of respiratory tract
  - tissue lesions, the order of toxicity is HF>HCl>HBr
- HI is predicted to be less toxic than HBr

Relative Toxicities [LC_{50} Values (ppm)] of HF, HCl, and HBr

Species	Exposure Duration	HF	HCl	HBr	Reference
Rat Mouse	5 minutes	18,200 6247	41,000 13,750		Higgins et al. 1972
Rat Mouse	30 minutes	2042	4700 2644		Rosenholtz et al. 1963 (HF); MacEwen and Vernot 1972 (HCl)
Rat Mouse	1 hour	1395 342	3124 1108		Wohlslagel et al. 1976
Monkey Rat Mouse	1 hour	1774 1278 501		 2858 814	MacEwen and Vernot 1970 MacEwen and Vernot 1972

Severity of Lesions of Region 2 of the Nasal Cavity of Rats Following Inhalation of 1300 ppm HF, HCl or HBr for 30 Minutes

Necrotic lesion	HF	HCl	HBr
Epithelial	2.0*	2.0*	0.9
Submucosal	0.3	0.4	0.0
Bone	0.0	0.0	0.0
Gland	0.0	0.0	0.0

Data from Stavert et al. 1991.
Based on eight rats/exposure group.
Severity index ranged from 1 to 4 with 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe.
*Statistically significant compared to air-exposed controls, $p<0.05$.

Base the AEGL values on analogy with HBr (support with data from HF and HCl) because of predicted similar toxicity and adequate data.

HI AEGL-1:
Based on slight irritation (NOAEL) in HBr study
1 of 6 subjects, 3 ppm for duration of a few minutes
Intraspecies uncertainty factor of 3 (below definition of AEGL-1, only 6 subjects)
Use same value across all exposure durations because there is adaptation to the slight irritation that defines the AEGL-1
HF: slight irritation at 3 ppm (intraspecies UF of 3)
HCl: no irritation in exercising asthmatics at 1.8 ppm (intraspecies UF of 1)

HI AEGL-2: (10 minutes)
Based on HCl 10-minute RD_{50} of 309 ppm
Multiplied by 0.3 to get "some sensory irritation"

HI AEGL-2: (30 minutes to 8 hours)
Based on severe nasal/pulmonary histopathology in rats exposed to 1300 ppm HF, HCl, or HBr for 30 minutes
Modifying factor of 3 to account for sparse data base for HCl, HBr AEGL-2
Inter- and intraspecies uncertainty factors of 3 each (=10)
Time scaling utilized empirical data from HCl lethality studies (n = 1)

HI AEGL-3:
Based on 1-hour HBr $BMCL_{05}$ of 1239 ppm for the rat
Inter- and intraspecies uncertainty factors of 3 each (=10)
Time scaling utilized empirical data from HCl lethality studies (n = 1)

Proposed Hydrogen Iodide AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm

Classification	Exposure Duration (Values in ppm)				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
HF	1	1	1	1	1
HCl	1.8	1.8	1.8	1.8	1.8
HBr, HI	1	1	1	1	1
AEGL-2					
HF	95	34	24	12	12
HCl	100	43	22	11	11
HBr, HI	100	43	22	11	11
AEGL-3					
HF	170	62	44	22	22
HCl	620	210	100	26	26
HBr, HI	740	250	120	31	31

ATTACHMENT 14

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFUR DICHLORIDE (CAS NO. 10545-99-0)

PRESENTED BY

KOWETHA DAVIDSON
ORNL STAFF TOXICOLOGIST

NAC/AEGL MEETING, SAN ANTONIO, TX
DECEMBER 10-12, 2003

SULFUR DICHLORIDE
CAS NO. 10545-99-0

PHYSICAL CHARACTERISTICS:

- Reddish-brown fuming or red viscous liquid
- Vapor pressure: 7.6 mm Hg @ -23°C
- Vapor density: 3.55 (air = 1)
- Boiling point:59.6°C
- Soluble in benzene and carbon tetrachloride
- Conversion: 1 ppm = 0.237 mg/m^3

DESCRIPTION

- Decomposes when heated rapidly to 59°C, in water, and in alcohol (products were not identified)
- ODOR: Pungent chlorine or sulfidy like
- ODOR DETECTION THRESHOLD: 0.0042 mg/m^3 (0.018 ppm)

HUMAN DATA

NO DATA ARE AVAILABLE TO CHARACTERIZE THE TOXICITY OF SULFUR DICHLORIDE IN HUMANS

ANIMAL DATA

NO DATA ARE AVAILABLE TO CHARACTERIZE THE TOXICITY OF SULFUR DICHLORIDE IN ANIMALS

DERIVATION OF AEGLs FOR SULFUR DICHLORIDE

DATA ARE NOT AVAILABLE TO DERIVE AEGL VALUES FOR ANY LEVEL OR EXPOSURE DURATION

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFUR CHLORIDE (CAS NO. 10025-67-9)

PRESENTED BY

KOWETHA DAVIDSON
Oak Ridge National Laboratory

NAC/AEGL MEETING, SAN ANTONIO, TX DECEMBER 10-12, 2003

1

SULFUR CHLORIDE CAS NO. 10025-67-9

COMMON SYNONYMS:
Sulfur monochloride, disulfur dichloride

PHYSICAL CHARACTERISTICS:

- Light amber to yellowish red, fuming, oily liquid
- Vapor pressure: 6.7 torr @ 20°C
- Vapor density: 4.66 (air = 1)
- Soluble in organic solvents
- Conversion: 1 ppm = 0.181 mg/m3

2

DESCRIPTION

- Decomposes primarily to hydrogen chloride, sulfur dioxide, and sulfur in water or moist environment
- ODOR: irritating, suffocating, penetrating, nauseating
- ODOR DETECTION THRESHOLD: No data

3

HUMAN DATA

- Irritation threshold: 2-66 ppm
- Considered an upper respiratory tract irritant in humans
- Upper respiratory tract irritation may be due to decomposition products

4

ANIMAL DATA

Bomhard et al., 2000

• **Study type**:	4-hour inhalation
• **Species/Strain**:	rat/strain not reported
• **Sex:**	males and females (5 of each sex/group)
• **Observation period**:	14 days
• **Endpoints**:	clinical signs, body weight, mortality, gross pathologic changes

5

Results

44 ppm	no effects
1016 ppm	no effects
7369 ppm	bloody and serous nasal discharge, breathing difficulty, piloerection, reduced activity, and ungroomed fur (signs of discomfort)
9511 ppm	same as 7369 ppm but probably more severe, no deaths

6

Results (Cont.)

13,800 ppm: 3/10 died, breathing difficulty, cyanosis, corneal opacity, necrosis in the nose; emphysema, pulmonary edema, effects in liver and spleen, gastrointestinal irritation.

15,842 ppm: 6/10 died; other effects same as described above

19, 248 ppm: 10/10 died; other effects same as described above

7

AEGL -1 VALUES

10 min	30 min	1 hour	4 hour	8 hour
20 ppm [3.6 mg/m^3]	20 ppm [3.6 mg/m^3]	16 ppm [2.9 mg/m^3]	10 ppm [1.8 mg/m3]	5.1 ppm [0.9 mg/m^3]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: NOEL for upper respiratory irritation, breathing difficulty, signs of discomfort in rats exposed to 1016 ppm for 4 hours				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 1				
Time Scaling: $C^n \times t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

8

AEGL -2 VALUES

10 min	30 min	1 hour	4 hour	8 hour
74 ppm [13 mg/m³]	74 ppm [13 mg/m³]	58 ppm [119 mg/m³]	37 ppm [6.7 mg/m³]	18 ppm [3.3 mg/m³]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: Upper respiratory irritation, breathing difficulty, signs of discomfort in rats exposed to 7369 ppm for 4 hours				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 2				
Time Scaling: $C^n \times t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

9

AEGL -3 VALUES

10 min	30 min	1 hour	4 hour	8 hour
180 ppm [33 mg/m³]	180 ppm [33 mg/m³]	143 ppm [26 mg/m³]	90 ppm [16 mg/m³]	45 ppm [8.1 mg/m³]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: Threshold for lethality (LC_{01} = 9014 ppm) for a 4-hour exposure; the LC_{01} is slightly below the highest conc. that did not cause death.				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 1				
Time Scaling: $C^n \times t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

10

DATA ADEQUACY FOR SULFUR CHLORIDE

Only one acute inhalation study was available for deriving AEGLs.

The study showed clear concentration-response relationships for lethal and non-lethal effects.

The report provided no information on exposure conditions, analytical verification of chamber concentrations, or estimates of decomposition products.

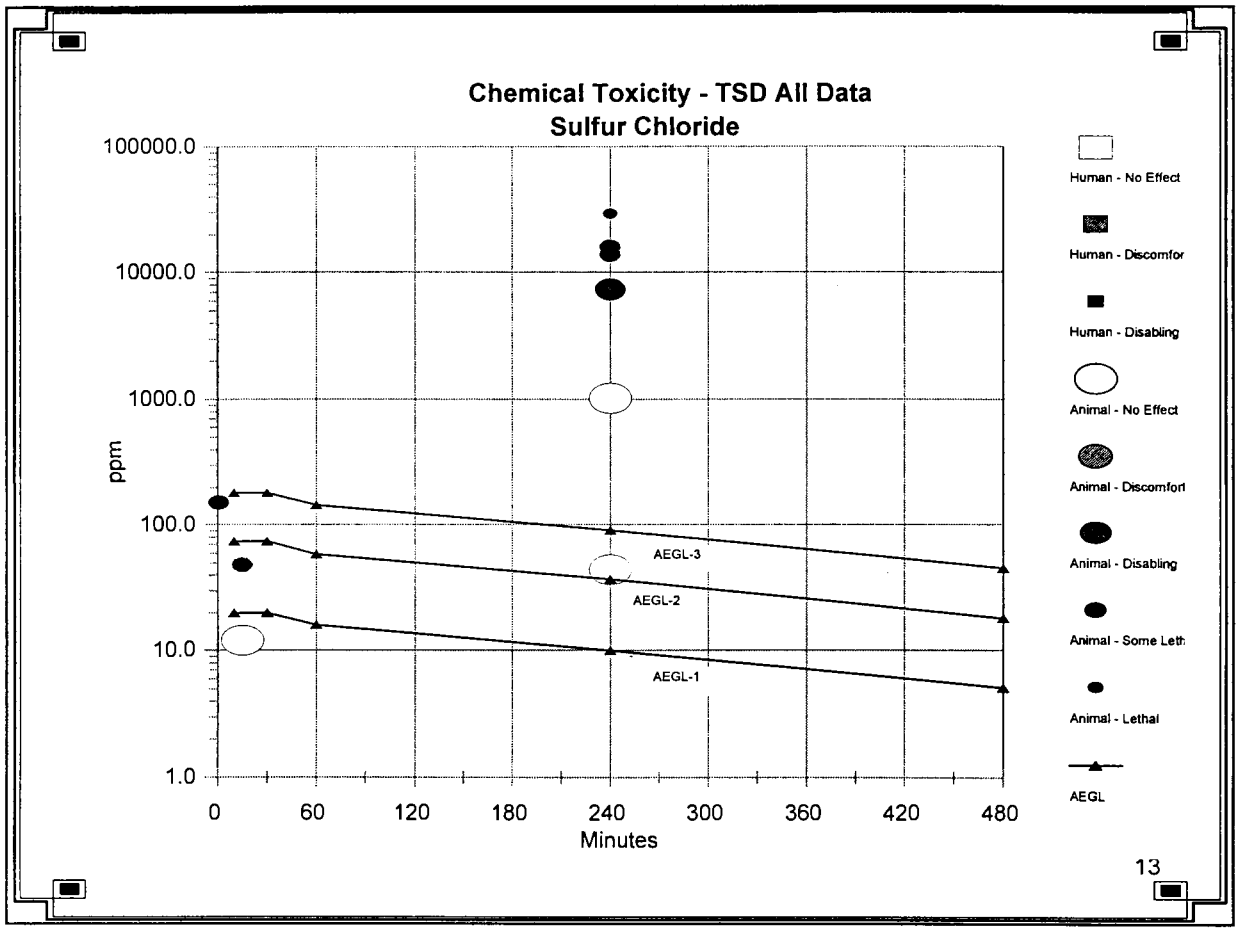
Default uncertainty factors were used in acknowledgment of the lack of additional data.

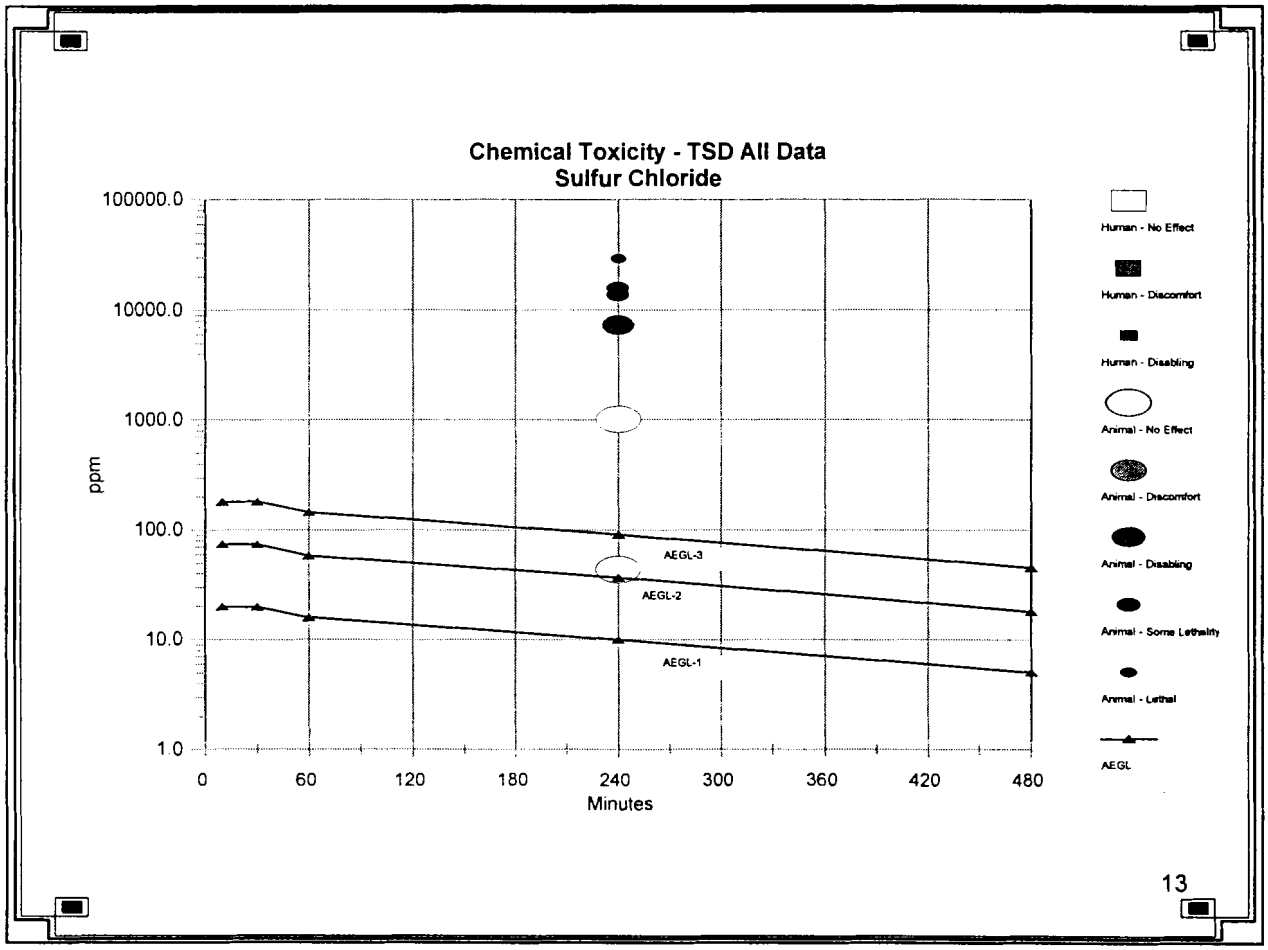
11

Proposed AEGL Values For Sulfur Chloride (ppm [mg/m^3])

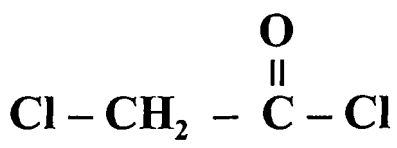
Class.	10 min.	30 min.	1 hour	4 hours	8 hours	Endpoint
AEGL-1	20 [3.6]	20 [3.6]	16 [2.9]	10 [1.8]	5.1 [0.9]	No effect level
AEGL-2	74 [13]	74 [13]	58 [11]	37 [6.7]	18 [3.3]	Upper respir. irrit. & dyspnea
AEGL-3	180 [33]	180 [33]	143 [26]	90 [16]	45 [8.1]	Lethality threshold

12


Chemical Toxicity - TSD All Data
Sulfur Chloride
100000.0
10000.0
1000.0
100.0
10.0
1.0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfor
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Leth
Animal - Lethal
AEGL
13


Chemical Toxicity - TSD All Data
Sulfur Chloride
100000.0
10000.0
1000.0
100.0
10.0
1.0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL
13

AEGLs for CHLOROACETYL CHLORIDE (CAC)



ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Steven Barbee
Chemical Reviewers: Nancy Kim and Robert Benson

- Chloroacetyl chloride (CAC) is a liquid with a pungent odor. It decomposes exothermally in water to produce chloroacetic acid and HCl.

- CAC major uses are as an intermediate in the synthesis of tear gas, chloracetamide herbicides, and pharamceuticals. In 1992 >45,000 metric tons were used industrially.

- CAC is corrosive to tissues and irritates the eyes, skin, and respiratory system. Secondary sources report the vapor can cause dyspnea, cough, cyanosis, laryngospasm, pulmonary edema, bronchospasm and bronchopneumonia.

CHLOROACETYL CHLORIDE (CAC)

HUMAN TOXICITY DATA

- **No acute lethality studies**

- **Odor Awareness**:
  - **0.011 ppm** was undetectable (1 hygienist; Dow, 1988b),
  - **0.023 ppm** was barely detectable ("")
  - **0.140 ppm** was "strong" ("")
  - **0.05 ppm,** collected over ≥7 hrs, was "readily apparent and objectionable" (Monsanto 1987)

- **Irritation:**
  - **0.91 ppm** was painful to the eyes and caused lacrimation (Dow 1988b)
  - **0.43 ppm** was threshold of irritation (Lim_{ir}) for humans "using subjective indicators" (Germanova et al. 1988). Exposure time not reported, possibly 1 min, per Izmerov et al. (1982) definition.

Chloracetyl Chloride Inhalation Single-Exposure Animal Studies					
Species	**Exp. time (Ref.)**	**Conc. [1] (ppm)**	**Mortality**		**Effects, Comments**
			M	**F**	
Rat	**1 hr (Dow '86)**	**32 [AEGL-2]**	**0/6**	**0/6**	▸ **Eye squinting, lacrimation during exposure; urine stains, initial weight loss**
		208	0/6	0/6	▸ As at 32 ppm but worse; also shallow breathing; lethargy, periocular red stains
		522	0/6	0/6	▸ As at 208 ppm but worse; labored breathing, gasping, salivation, red stains near muzzle
		747	5/6	1/6	▸ LC_{50} = 660[2] or 645[3] ppm for M; death on d. 2, 7, 8, 13 (F); toxicity as for 522 ppm but worse, lung edema or lungs don't collapse at necropsy, enlarged adrenals
Rat	2 hrs(Herzog'59)	108-6494 (N)	100% at ≥3462		▸ 80 animals tested, obs. 5 d.; sex, strain, # rats/group, and specific results not given.
Rat	4 hrs (Carp. '49)	1000 (N)	2/6, 3/6, or 4/6		▸ Animal sex and further methods and results details were not provided.
Rat	7 hrs 5-10 min	~2.5 ~4	0/? 0/?		▸ No visible effects; # and sex rats not stated ▸ Respiratory distress; "" (Dow'70a)
Mouse, white	2 hrs (Herzog 1959)	108 -6494 (N)	0/10 to 10/10		▸ LC_{50} = 1066 ppm; mice obs. only 5 days. All had upper respiratory irritation (rubbed mouth, half-open and watery eyes, dyspnea). Most lesions in trachea & lungs (edema, hemorrhage, necrosis). Tox. not stated for specific concs.
Guinea pig	2 hrs (Herz.'59)	108-6494 (N)	100% at ≥3462		▸ 50 animals; obs. 5 d. Sex, strain, #animals/ group, and specific results not given.

[1]Exposure concentrations are **analytical** unless stated otherwise (N=nominal).

TABLE 3. Chloracetyl Chloride Dow 1982 Multiple-Exposure Animal Study					
Species	**Exposure time**	**Conc. (ppm)**	**Mortality**		**Effects, Comments**
			M	**F**	
Rat	**4 wks, 6 hr/d, 5d/wk**	**0.5[2] [AEGL-1]**	**0/10**	**0/10**	▸ **Conjunctival redness after initial exp., olfactory epithelium inflammation**
		1.0	0/10	0/10	▸ As at 0.5 ppm but worse, nasal exudate, poor weight gain, lung lesions
		2.5	8/10	9/10	▸ As at 1 ppm but worse, lethargy, BW loss, lesions in nasal turbinates, trachea, and/or lungs (inflammation, hypertrophy, -plasia, metaplasia, necrosis, atrophy, pneumonitis or bronchitis). No death 1st wk.
		5.0	10/10	9/10	▸ As at 1 ppm but worse. No death 1st wk.
Mouse	**4 wks, 6 hr/d, 5d/wk**	0.5[2]	0/10	0/10	▸ Sneezing, conjunctivitis, resp. mucosa inflammation w. eosinophilic inclusions in nasal turbinates, trachea, and bronchi
		1.0	0/10	0/10	▸ As at 0.5 ppm but worse, poor weight gain
		2.5	0/10	2/10	▸ As at 1 ppm but worse, BW and fat loss, mucosal hypertrophy and hyperplasia. No death 1st wk.
		5.0	1/10	2/10	▸ As at 2.5 ppm but worse, rales, lethargy, nasal exudate, alveolar macrophages w. red cytoplasmic masses. No death 1st wk.
Hamster	**4 wks, 6 hr/d, 5d/wk**	0.5[2]	0/10	0/10	▸ Sneezing and closed eyes
		1.0	0/10	0/10	▸ As at 0.5 ppm but worse
		2.5	0/10	0/10	▸ As at 1 ppm but worse, poor weight gain
		5.0	0/10	0/10	▸ As at 2.5 ppm but worse, weight/fat loss

CHLOROACETYL CHLORIDE (CAC)

AEGL-1

Key Study: Dow 1982. Endpoint: Mild eye irritation (conjunctival redness) in rats after a single 6-hour exposure to ~1 ppm (0.84 ± 0.51 ppm).

Scaling: None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time

Total Uncertainty Factor: **10**

Interspecies: **3:** Eye conjunctivitis due to local contact irritation is not expected to vary greatly among animals

Intraspecies: **3:** Eye conjunctivitis due to local contact irritation is not expected to vary greatly among humans

AEGL-1 Values for Chloroacetyl Chloride (CAC)				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
0.08 ppm	0.08 ppm	0.08 ppm	0.08 ppm	0.08 ppm

- **AEGL-1 is supported by the limited human data:**
  - It is **>0.05 ppm**, which had an "objectionable" odor throughout a ≥7 hr work shift, but no any adverse health effects were reported.
  - It is ~10-fold below **0.9 ppm**, which was "painful" and caused lacrimation
  - It is comparable to **0.140 ppm**, which had "strong" odor but was not irritating to the eyes upon exposure for a few (??) minutes (noting that an intraspecies UF=3 would lower 0.14 ppm to **0.05 ppm**).

CHLOROACETYL CHLORIDE (CAC)

AEGL-2

Key Study: Dow 1986. Toxicity endpoint: eye lacrimation and eye squinting, which would impede the ability to escape. The point of departure was 32 ppm because the next higher conc. tested (208 ppm) was near the estimated lethality threshold of 215 ppm for rats.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <1 hr and n=1 for >1 hr, exc. for 8 hrs adopted 4-hr value because calculated 8-hr value (0.13 ppm) is near the AEGL-1 (0.08 ppm).

Total Uncertainty Factor: 30
Interspecies: 10: Data suggests humans are more susceptible to lacrimation from CAC exposure than animals**.
Intraspecies: 3: Lacrimation due to severe local contact irritation is not expected to vary greatly among humans.

[**0.9 ppm caused lacrimation and eye pain in human (??time), but rats, mice and hamsters exposed to 5 ppm for 6 hrs/day had conjunctivitis w/o lacrimation]

AEGL-2 Values for Chloroacetyl Chloride				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
1.9 ppm	1.3 ppm	1.1 ppm	0.27 ppm	0.27 ppm

- **AEGL-2 values are supported by the limited human data (see AEGL-1)**

CHLOROACETYL CHLORIDE (CAC)

AEGL-3

Key Study: Dow 1986. Toxicity endpoint: the lethality threshold, estimated as 215 ppm (1/3 of the LC_{50} for male rats)

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <1 hr and n=1 for >1 hr.

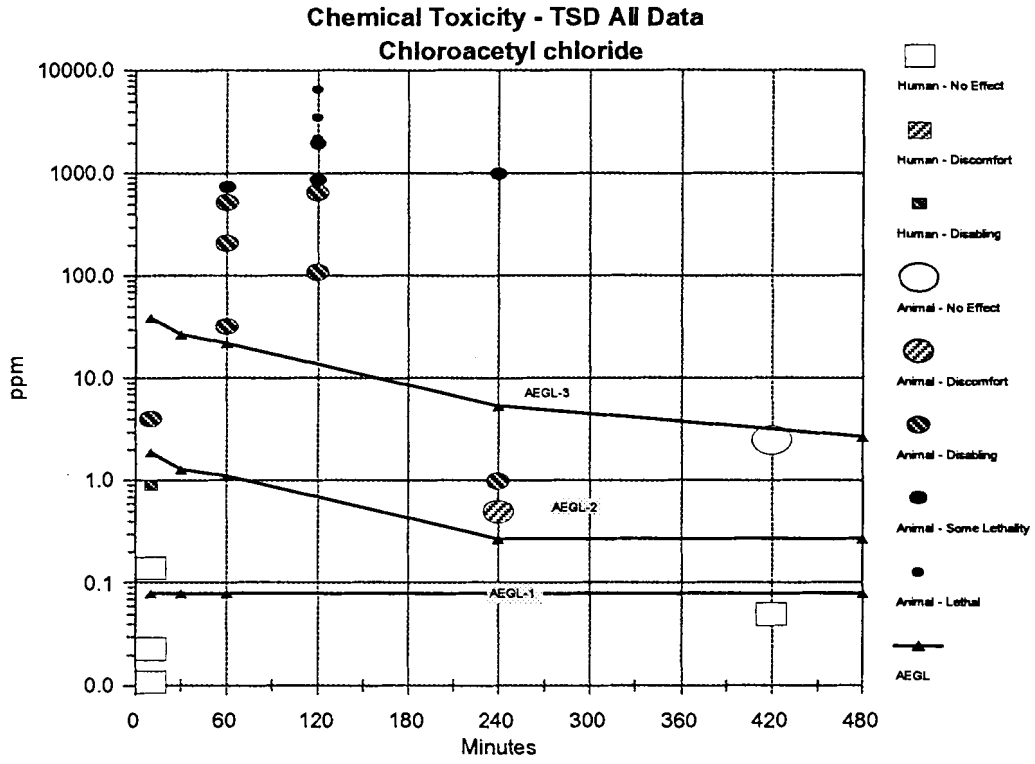
Total Uncertainty Factor: 10
Interspecies: 3: Lethality from respiratory lesions and having a steep dose-response occurred in several rat and mouse studies, at CAC concs. within a factor of 2-3
Intraspecies: 3: Threshold for lethality from direct destruction of respiratory tissue is not expected to vary greatly among humans, based on steep dose-response seen in the animal studies.

AEGL-3 Values for Chloroacetyl Chloride				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
39 ppm	27 ppm	21 ppm	5.4 ppm	2.7 ppm

Summary of AEGL Values for Chloroacetyl Chloride (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1[a] (Non-disabling)	**0.08**	**0.08**	**0.08**	**0.08**	**0.08**	**Conjunctival redness in rats (Dow 1982)**
AEGL–2 (Disabling)	**1.9**	**1.3**	**1.1**	**0.27**	**0.27**	**Lacrimation and eye squinting in rats (Dow 1986)**
AEGL–3 (Lethal)	**39**	**27**	**21**	**5.4**	**2.7**	**Threshold for lethality in male rats (Dow 1986)**

[a] Odor of 0.023 ppm was reported to be barely detectable by an industrial hygienist (Dow 1988b).

Category Plot for Chloroacetyl Chloride



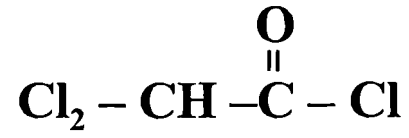
Notes:

1. For Dow 1982 multiple-exposure study, one 6-hour exposure to 0.5 ppm was entered as Category 1 (discomfort) for rats, mice, and hamsters. A single 6-hour exposure to 1 ppm was entered as Category 1 only for rats.

2. For Dow 1988b human study, exposure time was not defined, and was estimated to be 10 minutes for the Category plot.

3. Analytical concentrations are presented if available. No adjustments were made for discrepancies between nominal and analytical concentrations (latter were 45-82% lower than nominal in studies where both were stated).

AEGLs for DICHLOROACETYL CHLORIDE (DCAC)



ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Steven Barbee
Chemical Reviewers: Nancy Kim and Robert Benson

- Dichloroacetyl chloride (DCAC) is liquid with an acrid, penetrating odor. It decomposes in water to form HCl and dichloroacetic acid.

- DCAC is irritating to the eyes and mucous membranes. Acute exposure may cause dyspnea, chest pain, upper airway and pulmonary edema, bronchospasm, pneumonitis, airway hyper-reactivity, and chronic lung function abnormalities.

- DCAC production in the U.S. exceeds 1 million pounds annually; it is mainly used as a reactive intermediate.

- No standards or guidelines are currently available for DCAC air exposure.

DICHLOROACETYL CHLORIDE (DCAC)

HUMAN TOXICITY DATA

- ❑ **No acute lethality studies**

- ❑ **Non-lethal toxicity:** Dahlberg and Myrin (1971) described 10 welding shop scenarios; only two reported workers' responses (#3 and #6). DCAC (and phosgene) was formed from welding arc in air cont. trichloroethylene (TCE). Air samples collected 3 min, ~30 cm from the arc. Conclusions:

  - ❑ **0.1 ppm:** DCAC odor is recognized
  - ❑ **0.5-1 ppm:** exposures above this conc. not advisable; workers may tolerate for a time without complaining except of "bad smell,"
  - ❑ **10 ppm:** caused immediate coughing and eye irritation and is not endurable for long", and
  - ❑ **13 ppm:** "could certainly not be endured for 1 hr" **[Scenario 3]**

Shop	DCAC (ppm)	Phosg. (ppm)	TCE (ppm)	Scenario description
#3 [Near welding site; near vent]	13 0.5		256 248	Welding was ~ 10 m from spill of ~10 L TCE, which was swept into a drain. Simulated accident; ~1 hr exposure. Worker noticed unpleasant smell, left to vomit, came back, and lost consciousness. He was hospitalized and quickly regained consciousness. Afterwards, he had muscular pains and was "sick listed" for a "long time."
#6 [Before & after fan adjustment]	10.4 1.6	0.3 0.06	65 27	TCE source was 15-20 m from unventilated welding bench. All nearby noticed "very disagreeable smell" and the welder had several coughing attacks.

- ❑ Phosgene was produced at ~5x lower amount than DCAC. The welders' symptoms are believed due to DCAC because: (1) TCE has a sweet odor, detectable at ≥50 ppm, and (2) phosgene has a mild odor perceptible at 0.4 ppm, and causes throat and ocular irritation at ≥3.1- 4.8 ppm.

DICHLOROACETYL CHLORIDE (DCAC)

ANIMAL TOXICITY DATA

Acute Lethality:

- Range-finding test: 2/6 rats (M?) died after inhaling 2000 ppm DCAC for 4 hrs (nominal conc.; Smyth et al. 1951). Inferred that 0/6 died at 1000 ppm based on methodology [tested log series of concs. with a factor of two, and reported results only for fractional mortality]. No other effects reported.

- Smyth et al. (1951) exposed 6 rats to ~saturated DCAC vapor (30,000 ppm). Longest period survived by all rats was 8 minutes.

Nonlethal Toxicity:

- Carcinogenicity study: M rats (50/dose) given 30 exposures of 0.5, 1.0, or 2.0 ppm DCAC for 6 hours/day, 5 days/week had no mortality during treatment; 2/50 exposed to 2.0 ppm developed nasal carcinomas (none in control group; Sellakumar et al. 1987). Cageside observations, gross pathology, body weights not reported.

  The anterior respiratory epithelium was the most severely affected: saw necrosis, ulceration, acute inflammation, and in some cases squamous metaplasia and dysplasia.

DICHLOROACETYL CHLORIDE (DCAC)

AEGL-1

- **Not recommended due to insufficient data.** No human or animal studies were conducted in which endpoints consistent with the definition of AEGL-1 were reported.

- Exposure to 0.1 ppm DCAC, which was stated to have a recognizable odor in the welding shop study (Dahlberg and Myrin 1971), was not associated with a specific exposure duration or adverse health effects.

DICHLOROACETYL CHLORIDE (DCAC)

AEGL-2

Key Study: Welder shop scenario: workers exposed to ~1.6-10.4 ppm DCAC noticed a "very disagreeable smell" and the welder had several coughing attacks (Dahlberg and Myrin 1971). Exposure duration not reported; but est. as 10 min (each welding operation took only few min.)

Toxicity endpoints: Coughing and notable discomfort at 1.6 ppm

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; used n=1 to scale to 30 min. Same value adopted for 30 min to 8 hrs because scaling to ≥ 1 hr yielded concs. below those recognized by workers (i.e. 0.1 ppm).

Total Uncertainty Factor: 3

Interspecies: Not applicable

Intraspecies: 3: The key toxic endpoint (coughing; notable discomfort) is not likely to be significantly worse in the general population than in repeatedly exposed workers.

AEGL-2 Values for DCAC				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.53 ppm	0.18 ppm	0.18 ppm	0.18 ppm	0.18 ppm

- ❑ Key study also states that exposures to >0.5-1 ppm are "not advisable" but may be tolerated "for a time" w/o complaining except of "bad smell".

DICHLOROACETYL CHLORIDE (DCAC)

AEGL-3

Key Study: Smyth et al. (1951) range-finding test: 2/6 rats exposed to 2000 ppm for 4 hours died, whereas 0/6 rats died at 1000 ppm (nominal concentration; estimate 500 ppm as analytical concentration), which is an estimated lethality threshold. No results other than death were reported.

Toxicity endpoint: The estimated lethality threshold (500 ppm)

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; used n=3 and n=1 to extrapolate to < 4 hours and > 4 hours, respectively, except 30-min values were adopted as 10-min values.

Total Uncertainty Factor: 100
Interspecies: 10: Only one species tested; cause of death in key study not defined.
Intraspecies: 10: Because cause of death in the key study was unknown, variability among humans cannot be reliably estimated.

Modifying factor: 2: The analytical conc. was not provided, and may be half the nominal conc. based on study with related compd. CAC

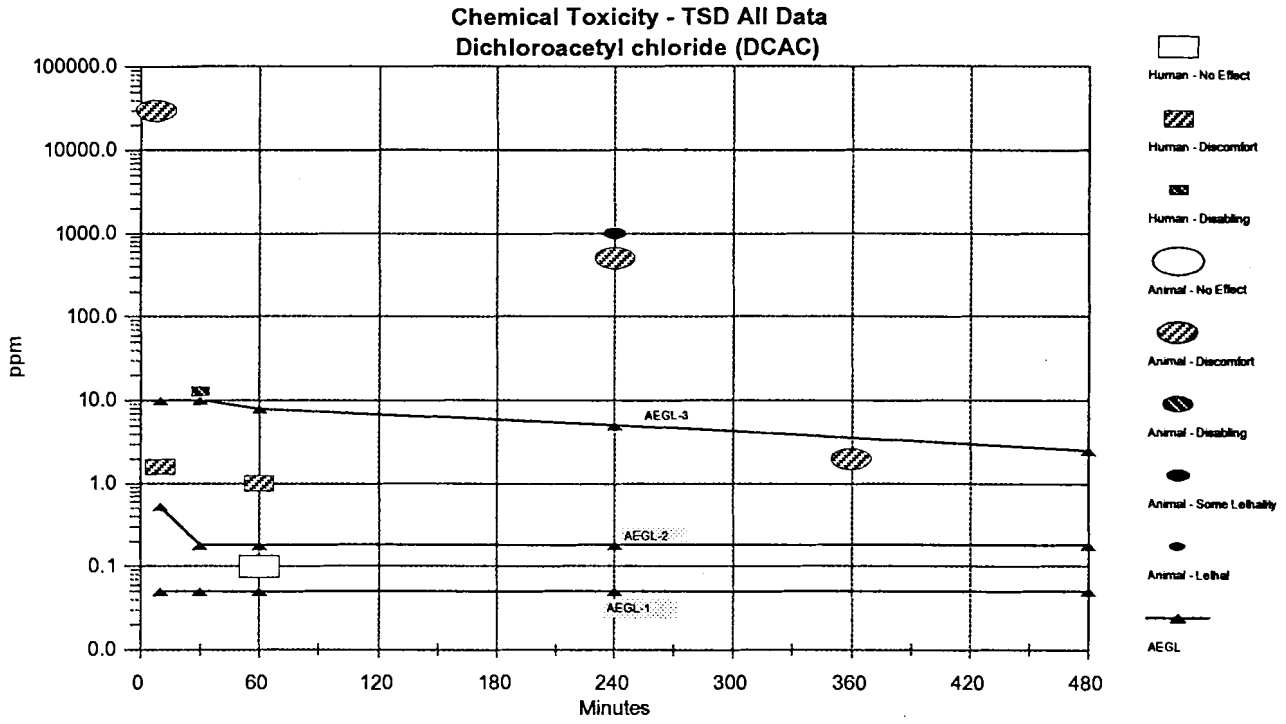
AEGL-3 Values for DCAC				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
10 ppm	10 ppm	7.9 ppm	5.0 ppm	2.5 ppm

- AEGL-3 values are consistent with human welder scenario, in which a worker exposed to ~13 ppm for ~1 hr lost consciousness, recovered in hospital, but had muscular pains and was unable to work for a long time.

Summary of AEGL Values for DCAC						
Classifi-cation	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1[a] (Non-disab)	**Not recommended due to insufficient data.**					
AEGL–2 (Disabling)	**0.53**	**0.18**	**0.18**	**0.18**	**0.18**	Coughing and notable discomfort in workers (Dahlberg and Myrin '71)
AEGL–3 (Lethal)	**10**	**10**	**7.9**	**5.0**	**2.5**	Threshold for lethality in rats (Smyth et al. 1951)

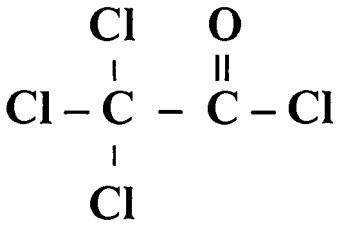
[a] Odor is recognized at 0.1 ppm.

Category Plot for Dichloroacetyl Chloride



Note: AEGL-1 values were not recommended due to insufficient data; but assumed a value of 0.05 to be able to generate this plot.

AEGLs for **TRICHLOROACETYL CHLORIDE (TCAC)**



ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Robert Benson
Chemical Reviewers: Nancy Kim and Steven Barbee

- TCAC is a corrosive liquid with a pungent odor. Decomposes in water to produce trichloroacetic acid and hydrochloric acid (HCl)

- Used as intermediate in organic synthesis; no information on annual production volume

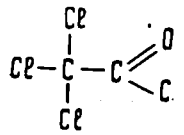
- No odor threshold data, air standards, or guidelines available

- Causes irritation of the eyes, skin, and respiratory system, possibly leading to spasm, inflammation, edema of the larynx or bronchi, chemical pneumonitis, and pulmonary edema.

TRICHLOROACETYL CHLORIDE (TCAC)

AEGL-1, AEGL-2, and AEGL-3 values <u>not recommended</u> due to insufficient data.

The only available data was a secondary report (Izmerov et al. 1982) that provided no details of the study methods or results, and which was not considered appropriate for AEGL derivation.

Trichloroacetyl chloride+  MAC_{ws} 0.1 (v), Class I 248, 461	Intragastric: LD_{50} rat 600 Inhalation: LC_{50} rat 475 (318—698) 4 h, LC_{50} mouse 445 (296—667); Lim_{ac} rat 10 4 h (1, 11, 15), Lim_{ac} rat 1—3 4 h (7, 9); Lim_{ir} man 0.6 Has irritant properties Detection: colorimetry; detection limit 0.1 μg in analytical volume

TCAC : Data from *Izmerov et al. 1982*

- Lim_{ir} (irritation threshold) for humans was 0.08 ppm. This was not used to derive AEGL-1 values because the original study and methods details were unavailable, and the exposure duration (1 minute) was insufficient.

[**Lim_{ir}** = "the threshold of irritant action on the mucous membranes of the upper airways and eyes. Values for man are based on subjective sensations for exposures lasting 1 min unless stated otherwise."]

- LC_{50} of 64 and 60 ppm were reported for 4-hr exposure for rats and mice. These stand-alone values were not used to derive AEGL-3 values because the original study (with the respective methods and results details) was unavailable.

- For the same reason, the stand-alone LC_{50} values were not used to derive AEGL-2 values by applying an adjustment factor.

TCAC : Data from *Izmerov et al. 1982*

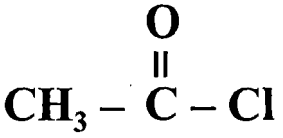
- Lim_{ac} ("threshold of acute effect") for rats for 4-hr exposure was 1.34 ppm [based on changes in the summation threshold index, rectal temperature, and motor activity] and 0.13-0.40 ppm [based on changes in respiration rate and lung staining].

- While some of these effects may be within the scope of AEGL-2, the lack of methods and results details precluded use of the data for AEGL-2 derivation.

[**Lim_{ac}** = "lowest concentration (dose) that causes such a change in a particular biochemical index in a whole organism which is beyond the latter's capacity for physiological adaptation."]

THEREFORE: AEGL-1, AEGL-2, and AEGL-3 values were NOT recommended due to insufficient data.

AEGLs for ACETYL CHLORIDE (AC)



ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Steven Barbee
Chemical Reviewers: Nancy Kim and Robert Benson

- ✓ AC is a colorless, flammable, fuming liquid with a pungent odor
- ✓ Decomposes in water to form hydrogen chloride (HCl) and acetic acid
- ✓ AC is a severe eye and respiratory tract irritant. Can cause spasm, inflammation, and edema of larynx and bronchi, chemical pneumonia, pulmonary edema.
- ✓ Has many uses as acetylating agent, e.g. in pharmaceutical manufacture. No data for U.S. production volume; U.S. market is ~ 500 tons annually.

ACETYL CHLORIDE (AC)

AEGL-1, AEGL-2, and AEGL-3 values <u>not recommended</u> due to insufficient data.

HUMAN TOXICITY DATA

✓ No quantitative Acute Lethality data were located.

✓ No odor threshold data

✓ No air standards or guidelines are currently available.

✓ Two anecdotal (i.e. no experimental data) reports:
- ✓ Inhalation of 2.3 ppm AC for one min was intolerable (NAMCC 1961)
- ✓ 0.5 ppm AC causes lacrimation and a burning sensation in eyes, nose, and throat (Wagner 2002; no additional details provided.

ANIMAL TOXICITY DATA

✓ **No animal studies with AC were located.**

Summary of AEGL Values for Chloroacetyl Chloride (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1[a] (Non-disabling)	**0.08**	**0.08**	**0.08**	**0.08**	**0.08**	**Conjunctival redness in rats (Dow 82)**
AEGL–2 (Disabling)	**1.9**	**1.3**	**1.1**	**0.27**	**0.27**	**Lacrimation and eye squinting in rats (Dow 86)**
AEGL–3 (Lethal)	**39**	**27**	**21**	**5.4**	**2.7**	**Threshold for lethality in male rats (Dow 86)**

[a]Odor of 0.023 ppm was barely detectable; 0.05 ppm was "objectionable"; 0.14 ppm was "strong" to an industrial hygienist.

Summary of AEGL Values for DCAC						
Classifi-cation	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1[a] (Non-disab)	**Not recommended due to insufficient data.**					
AEGL–2 (Disabling)	**0.53**	**0.18**	**0.18**	**0.18**	**0.18**	Coughing and notable discomfort in workers (Dahlberg and Myrin '71)
AEGL–3 (Lethal)	**10**	**10**	**7.9**	**5.0**	**2.5**	Threshold for lethality in rats (Smyth et al. 1951)

[a] Odor is recognized at 0.1 ppm.

TABLE X-1. Comparison of physical, chemical, and toxicological values for the acetyl chlorides and their hydrolysis products					
Parameter	**Acetyl chloride (AC)**	**Chloroacetyl chloride (CAC)**	**Dichloroacetyl chloride (DCAC)**	**Trichloroacetyl chloride (TCAC)**	**HCl**
Molecular weight (CAS#)	78.50 (75-36-5)	112.94 (79-04-9)	147.39 (79-36-7)	181.83 (76-02-8)	36.46 (7647-01-0)
Solubility in water	decomposes	decomp. $t_{1/2}$ <30min	decomposes, $t_{1/2}$ 0.004 min	decomposes; 9.49 g/L @ 25°C	soluble
Vapor pressure	287 mm Hg @25°C	20 mm Hg @ 21°C	23mm Hg @ 25°C	21.3mm Hg@ 25°C	4.0 @ 17.8°C
Vapor density (air =1)	2.7	3.9	5.1	Not found	1.639
Liquid density (H_2O=1)	1.11	1.42 @ 20°C	1.5315 @ 16°/4°C	1.654 @ 0°/4°C	1.19 (38% soln.)
Odor and Irritation data (ppm)	no odor data; h: 0.5 lacrimation, 2.3 1 min intolerable	pungent; h: 0.023 barely detect; 0.9 lacrimation, pain	acrid; recog 0.1 ppm	no odor data; h: 0.08 is 1 min irrit. threshold	odor thr 1-5; ≥5 irr.; 50-100 max tol. for prolonged period
Lethality data – LC_{50}	not found	660 rat 1 hr	>2000 ppm 4 hr rat	rat 64ppm 4h; mus 60 ppm ??h	Rat 1 hr 3124; mus 1 hr 1108
Lethality data – LD_{50}	rat 910 mg/kg		2460 mg/kg	600 mg/kg rat	900 mg/kg rabbit
Corresponding ACID	**acetic**	**chloroacetic**	**dichloroacetic**	**trichloroacetic**	
Molecular weight (CAS#)	60.06 (64-19-7)	94.5 (79-11-8)	128.94 (79-43-6)	163.39 (76-03-9)	
pKa (pH 0.1 M solution)	4.756	2.87 (pH 1.93)	1.26	0.51 (pH 1.2)	None (<0; completely dissociates)
Water solubility	infinite; miscible	6.14 kg/L	1 kg/L	1.3 kg/L	
Vapor density (air =1)	2.07	3.26	4.45	Not available	
Liquid density (H_2O=1)	1.049	1.404	1.5724	1.6298	
Vapor pressure (mmHg)	11.4@20°C	0.06 @25°C	0.18 @25°C	4.54E-9 @25°C,	
Odor and Irritation data (ppm)	pungent; TCLo hum 816	~vinegar, 50% recog 0.045; Irrit h: 1.48; rat 6.16, NOEL 0.31, 0.13	H recog 0.04	H recog 0.24-0.37	
Lethality data – LC_{50} (ppm)	LCLo rat 16,000 4 h mus LC50 5620 1h	rat 47 ppm 4 hr	not found	rat, rabbit, cat, g. pig 4 hrs >4800 ppm	
Lethality data – LD_{50} (mg/kg)	3310 mg/kg rat	rat 108, 76, 580; pig 80 mg/k; 165 mg/kg	2820 mg/kg rat	dog 1600-2000, rat 3310-6900, mus 4970	

NAC-AEGL Meeting

Sulfuric acid, sulfurtrioxide, and oleum

Progress report - December 2003

rivm

National Institute for Public Health and the Environment

Why this progress report

- TSD currently under development
- huge database, not analysed all the data yet
- four specific issues need to be addressed now:
  - AEGL values only to be developed for sulfuric acid mist?
  - Ammonia in the oral cavity
  - Deposition aera of aerosols (hydroscopic growth; mouth breathing)
  - suitability of the guinea pig as an animal model

1: Sulfuric acid, sulfurtrioxide, and oleum

- H_2SO_4 - SO_3
- oleum: a mixture of H_2SO_4 and SO_3, usually between 10-70% SO_3; fuming sulfuric acid
- SO_3 in ambient air reacts rapidly with water to form sulfuric acid mist
- Any residual inhaled SO_3 reacts instantly with moist air in the respiratory tract or ultimately with the mucous membranes
- Thus, respiratory tissues are exposed to H_2SO_4, not to SO_3
- Proposal:
  - H_2SO_4, SO_3, and oleum are discussed in one TSD and AEGL-values are established only for sulfuric acid mist

rivm

Toxicological database

- Many controlled human volunteers studies available (46) for AEGL-1 development (and maybe AEGL-2)
- In addition 16 occupational / epidemiologic studies
- Animal data are important for AEGL-3 (and perhaps AEGL-2)
- Non-lethal tox: dozens of guinea pig studies, much less studies with other animals
- Lethal tox: 3x rat, 3x mouse, 3x rabbit, 9x guinea pig (only guinea pigs: young vs. old animals)

rivm

2: Neutralisation by respiratory ammonia

- Ammonia in breath: formation due to bacterial activity in the oral cavity
- Gaseous ammonia in breath (~150-1500 µg/m³) neutralises H_2SO_4 to ammoniumsulfate or ammoniumbisulfate
- Nearly all controlled human volunteer studies used pre-exposure gargling with citric acid to deplete oral/respiratory ammonia
- Ammonia concentration in exhaled air can be depleted to 2-20% and may return to 50% of baseline levels after 1 h (Norwood)
- Respiratory effects are enhanced by at least a factor 2 when subjects gargled citrus juice (Utell: MMAD 0.8 µm))
- Conclusion: Gargling with citrus juice make subjects sensitive - no intraspecies UF is needed (for small particles?)

rivm

3: Deposition of sulfuric acid aerosols

Exposure to sulfuric acid is exposure to aerosols

Amount and region of deposition is *a.o.* dependent on:

- particle size
- nose versus mouth breathing
- ventilation rate (exertion/escape)
- species

- Complicating factor:
  - hygroscopicity of sulfuric acid aerosols
  - particles continue to grow in the respiratory tract
- Usually no specific data on deposition area available
  - For sulfuric acid we do have such data (experimental & models) - should we use it for AEGL development? How?

rivm

Deposition: basic topics *(EPA, 1996)*

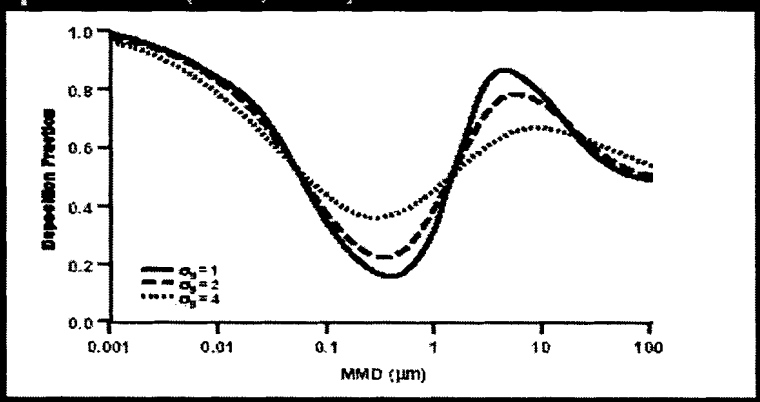
Different mechanisms are involved in particle deposition. The impact of each mechanism on total deposition and region of deposition considerably depend on the particle size.

Three regions:

- ET: extrathoracic region
  - nasal passage, pharynx, larynx
- TB: tracheobronchial region
- A: alveolar region

rivm

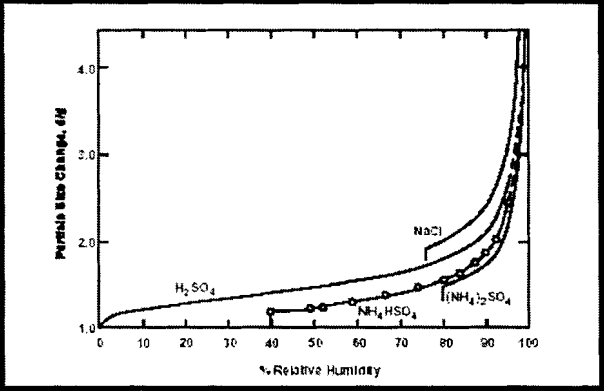
Deposition *(EPA, 1996)*



Calculated mass deposition from polydisperse aerosols of unit density with various geometric standard deviations as a function of mass median diameter (MMD) for quiet breathing (tidal volume = 750 mL, breathing frequency = 15 min^{-1}).

rivm

Deposition of hygroscopic particles



Theoretical growth curves for sodium chloride, sulfuric acid, ammoniumbisulfate, and ammonium sulfate aerosols in terms of the initial and final size of the particle. Note that the H_2SO_4 curve, unlike those for the three salts, has no deliquescence point.

rivm

Mouth breathing versus nose breathing

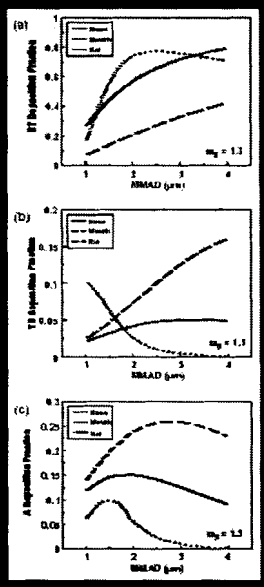
Mouth breathing causes change in:

- Absolute amount deposited
  - larger absolute amount of particles that reaches TB and A region
- Regional deposition
  - deposition of larger particles in TB and A region

rivm

Mouth breathing versus nasal breathing

Predicted extrathoracic deposition fractions versus mass median aerodynamic diameter (MMAD) of inhaled monodisperse aerosols for humans (nose versus mouth breathing) and rats (obligatory nose breathers), for
(a) the extrathoracic region,
(b) tracheobronchial region, and
(c) alveolar region.



rivm

Summary and implications *(EPA, 1996)*

- The amount and region of deposition depends on particle size, hygroscopic growth is an important factor
- Significant differences between deposition in animals and humans
- Interpretation of animal and human experiments
  - animal experiments: different growth rate due to shorter residence times
  - exposure conditions in human experiments
    - (gargling acid juices)
    - mouth vs. nasal breathing (mouthpiece, environmental chamber)
    - particle size
- Derivation of AEGL values

rivm

Summary and implications *(EPA, 1996)*

- Human volunteer studies: can we focus on studies with a certain range of particle sizes?
  - i.e. is anyone aware of a specific range of particle sizes relevant for chemical incidents?
- Human volunteer studies: can we focus on mouth or nose breathing regarding certain effects?
  - mouthpiece studies worst case for respiratory effects
  - chamber studies important to reveal other effects (e.g. eye irritation, nasal irritation)
- Extrapolation of animal experiments to humans as to particle size distribution
  - use defaults UF's or derive specific interspecies extrapolation factors?
  - Can we extrapolate such factors based on AEGL-1 (or -2) effects to the AEGL-3 situation?

rivm

4: What to do with the guinea pig?

- Guinea pig much more susceptible than other laboratory animal species
- Acute lethality (7-8 h exposures):
  - guinea pig LC_{50} ~ 20 (young) - 50 (old) mg/m^3
  - mouse LC_{50} ~ 600-700 mg/m^3
  - rabbit LC_{50} ~ 1600 mg/m^3
  - rat LC_{50} no reliable data
- 8-hour AEGL-3 based on guinea pig will be comparable to TLV (8-TWA) of 1 mg/m^3 → not realistic compared to human data
- sensitivity guinea pig due to involuntary bronchoconstriction to the point of death

rivm

What to do with the guinea pig

- Also for non-lethal toxicity the guinea pig is far more sensitive than other laboratory animals
- Other authors suggest that guinea pigs may be a useful model for asthmatics (who are sensitive to respiratory irritants)
- Unlike other rodents, guinea pigs can (and do) breath though their mouth

From guinea pig to man

- Guinea pig
  - 100-1000 µg/m^3 caused dose-related increase in airway resistance (Amdur)
- Normal subjects
  - 1000 µg/m^3 causes no response (many studies)
- Adult exercising asthmatics
  - 450-1000 µg/m^3 for 16 min causes dose-related increase in airway resistance: 100 µg/m^3 causes no response (Utell)
- Adolescent exercising asthmatics
  - 68-100 µg/m^3 for 40 min with 10 min exercise causes increase in airway resistance (Koenig)

What to do with the guinea pig?

- Our proposal:
  - the guinea pig will not be used as a model for lethal toxicity
  - the guinea pig data are valid for non-lethal toxicity and may serve as a model for asthmatics
  - guinea pigs and adolescent asthmatics seem to be equally susceptible: no interspecies UF needed.
  - Young asthmatics represent a susceptible subpopulation, so no intraspecies UF is needed

rivm

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR METHACRYLONITRILE

NAC/AEGL-31
December 10-12, 2003
San Antonio, TX

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rodgers

Chemical Reviewers: Ernest Falke and George Rusch

Mechanism of Toxicity

Metabolic release of cyanide via cytochrome P450 hydroxylation through an epoxide intermediate

HISTORY OF METHACRYLONITRILE TSD

First discussed at the September, 1998, NAC meeting

Subsequently discussed by the COT subcommittee in March, 2001.

Suggestions made by the COT subcommittee have been incorporated into the revised TSD.

MAJOR CONCERN:

Proposed values were not consistent with the overall data set.

Modifications are as follows:

AEGL-1 values are now derived.

AEGL-2 values are based on chemical-specific data, not AEGL-3 divided by 3.

AEGL-3 is not based on mouse data, but is based on rat data because mouse data yielded values inconsistent with the human irritation data.

Time scaling is done with n= 1 or n= 3 (default), not the cyanide 'n' value of n= 2.6.

Summary of Proposed AEGL Values for Methacrylonitrile:MARCH, 2001						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Insufficient data to derive AEGL-1 values
AEGL-2	1.5 ppm	1.5 ppm	1.1 ppm	0.70 ppm	0.50 ppm	⅓ of the AEGL-3 values
AEGL-3	4.5 ppm	4.5 ppm	3.4 ppm	2.0 ppm	1.5 ppm	4-hr no-effect-level for death in mice (Pozzani et al., 1968)

AEGL-1 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
2 ppm	2 ppm	2 ppm	2 ppm	2 ppm

Species:	Human (7-9/group)
Concentration:	2 ppm
Time:	10 minutes
Endpoint:	Transient nasal, ocular, or throat irritation
Reference:	Pozzani et al., 1968

Time Scaling: Concentration held constant across all time points because mild irritant effects generally do not vary greatly over time.

Uncertainty Factors:

Interspecies = 1 Subjects were human

Intraspecies = 1 Considered sufficient because:

Similar transitory irritation was noted at 14 ppm, a concentration 7-fold higher than the point of departure for the AEGL-1 values.

AEGL-2 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
22 ppm	22 ppm	18 ppm	11 ppm	7.5 ppm

Species: Rat (22-23/pregnant/group)
Concentration: 100 ppm
Time: 6 hours/day, GD 6-20
Endpoint: 13-15% decreased fetal body weight; Maternal NOEL
Reference: Saillenfait et al., 1993

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute, 1-hour, and 4-hour time periods, and $n = 1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-2 was also adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 3 Considered sufficient because:

Use of the full uncertainty interspecies factor of 10, would yield AEGL-2 values that are not consistent with the total data set: 7.6 ppm for 10- and 30-minutes, 6.1 ppm for 1-hour, 3.8 ppm for 4-hours, and 2.5 ppm for 8-hours. However, humans exposed to 14 ppm methacrylonitrile for 10 minutes experienced only transient ocular, nasal, or throat irritation (Pozzani et al., 1968).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 10

AEGL-3 VALUES: METHACRYLONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
32 ppm	32 ppm	25 ppm	13 ppm	13 ppm

Species: Rat (6/sex/group)
Concentration: 176 ppm
Time: 3 hours
Endpoint: No mortality; loss of consciousness
Reference: Pozzani et al., 1968

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 4-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 was also adopted as the 10-minute value. The 4-hour value was adopted as the 8-hour value because extrapolation would yield an 8-hr AEGL-3 value less than the 8-hour AEGL-2 value.

Uncertainty Factors:

Interspecies = 3 Considered sufficient because:

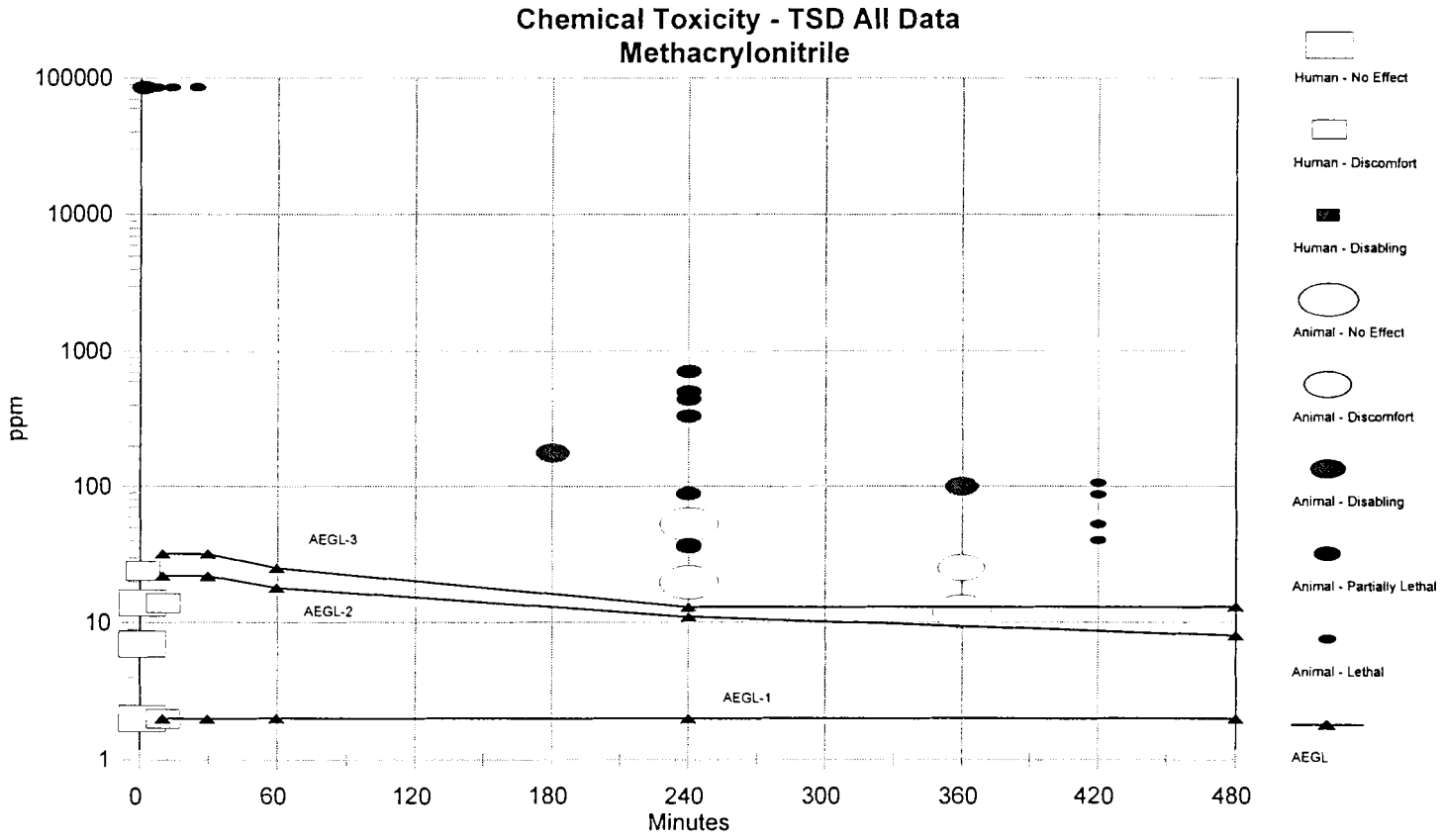
Use of the full uncertainty interspecies factor of 10, would yield AEGL-3 values that are not consistent with the total data set: 11 ppm for 10- and 30-minutes, 8.5 ppm for 1-hour, 4.4 ppm for 4-hours, and 2.2 ppm for 8-hours. However, humans exposed to 14 ppm methacrylonitrile for 10 minutes experienced only transient ocular, nasal, or throat irritation (Pozzani et al., 1968).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 10

EXTANT STANDARDS AND GUIDELINES FOR METHACRYLONITRILE					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	2.0 ppm	2.0 ppm	2.0 ppm	2.0 ppm	2.0 ppm
AEGL-2	22 ppm	22 ppm	18 ppm	11 ppm	7.5 ppm
AEGL-3	32 ppm	32 ppm	25 ppm	13 ppm	13 ppm
REL-TWA (NIOSH)	-	-	-	-	1 ppm
TLV-TWA (ACGIH)	-	-	-	-	1 ppm


Chemical Toxicity - TSD All Data
Methacrylonitrile
100000
10000
1000
100
10
1
ppm
AEGL-3
AEGL-2
AEGL-1
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR BENZONITRILE

NAC/AEGL-31
December 10-12, 2003
San Antonio, TX

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rodgers

Chemical Reviewers: Ernest Falke and George Rusch

Mechanism of Toxicity

Unlike the other nitriles considered, cyanide IS NOT a metabolite of benzonitrile.

No information regarding the mechanism of toxicity of benzonitrile was located.

Symptoms of acute poisoning are similar to those produced by other uncoupling agents, such as pentachlorophenol and dinitrophenol:

> **Fatigue, excessive sweating, thirst, pyrexia, anxiety, tachycardia, and hyperventilation**

Rat and mouse data have suggested signs of narcosis

AEGL-1 VALUES: BENZONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
19 ppm	19 ppm	15 ppm	3.8 ppm	2.0 ppm

Species: Rat (6 males/group)
Concentration: 900 ppm
Time: 1-hour
Endpoint: Irritation of extremities
Reference: MacEwen and Vernot, 1974

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute time period, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-1 was also adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 10 The rat is not the most sensitive species

Intraspecies = 3 Steep concentration-response curve implies little individual variability.

Mice exposed via inhalation (10% mortality for mice exposed to 890 ppm for 2 hr [ct = 1780 ppm·hr] vs. 100% mortality for mice exposed to 700 ppm for 4 hr [ct = 2800 ppm·hr] (MacEwen and Vernot, 1974).

Rats exposed orally (0.6 g/kg, 0/4 deaths vs. 2.0 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Rabbits exposed dermally (0.9 g/kg, 0/4 deaths vs. 1.4 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Modifying Factor = 2 Sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974)

AEGL-2 VALUES: BENZONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
27 ppm	27 ppm	22 ppm	12 ppm	5.5 ppm

Species: Rat (6 males/group)
Concentration: 900 ppm
Time: 3-hour
Endpoint: Labored breathing; poor coordination
Reference: MacEwen and Vernot, 1974

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-2 was also adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 10 The rat is not the most sensitive species

Intraspecies = 3 Steep concentration-response curve implies little individual variability.

Mice exposed via inhalation (10% mortality for mice exposed to 890 ppm for 2 hr [ct = 1780 ppm·hr] vs. 100% mortality for mice exposed to 700 ppm for 4 hr [ct = 2800 ppm·hr] (MacEwen and Vernot, 1974).

Rats exposed orally (0.6 g/kg, 0/4 deaths vs. 2.0 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Rabbits exposed dermally (0.9 g/kg, 0/4 deaths vs. 1.4 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Modifying Factor = 2 Sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice (MacEwen and Vernot, 1974)

AEGL-3 VALUES: BENZONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
71 ppm	71 ppm	56 ppm	23 ppm	11 ppm

Species: Mouse (10 males/group)
Concentration: 890 ppm
Time: 2-hours
Endpoint: 10% Mortality (1/10)
Reference: MacEwen and Vernot, 1974

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-3 was also adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 3 The mouse is the most sensitive species

Intraspecies = 3 Steep concentration-response curve implies little individual variability.

Mice exposed via inhalation (10% mortality for mice exposed to 890 ppm for 2 hr [ct = 1780 ppm·hr] vs. 100% mortality for mice exposed to 700 ppm for 4 hr [ct = 2800 ppm·hr] (MacEwen and Vernot, 1974).

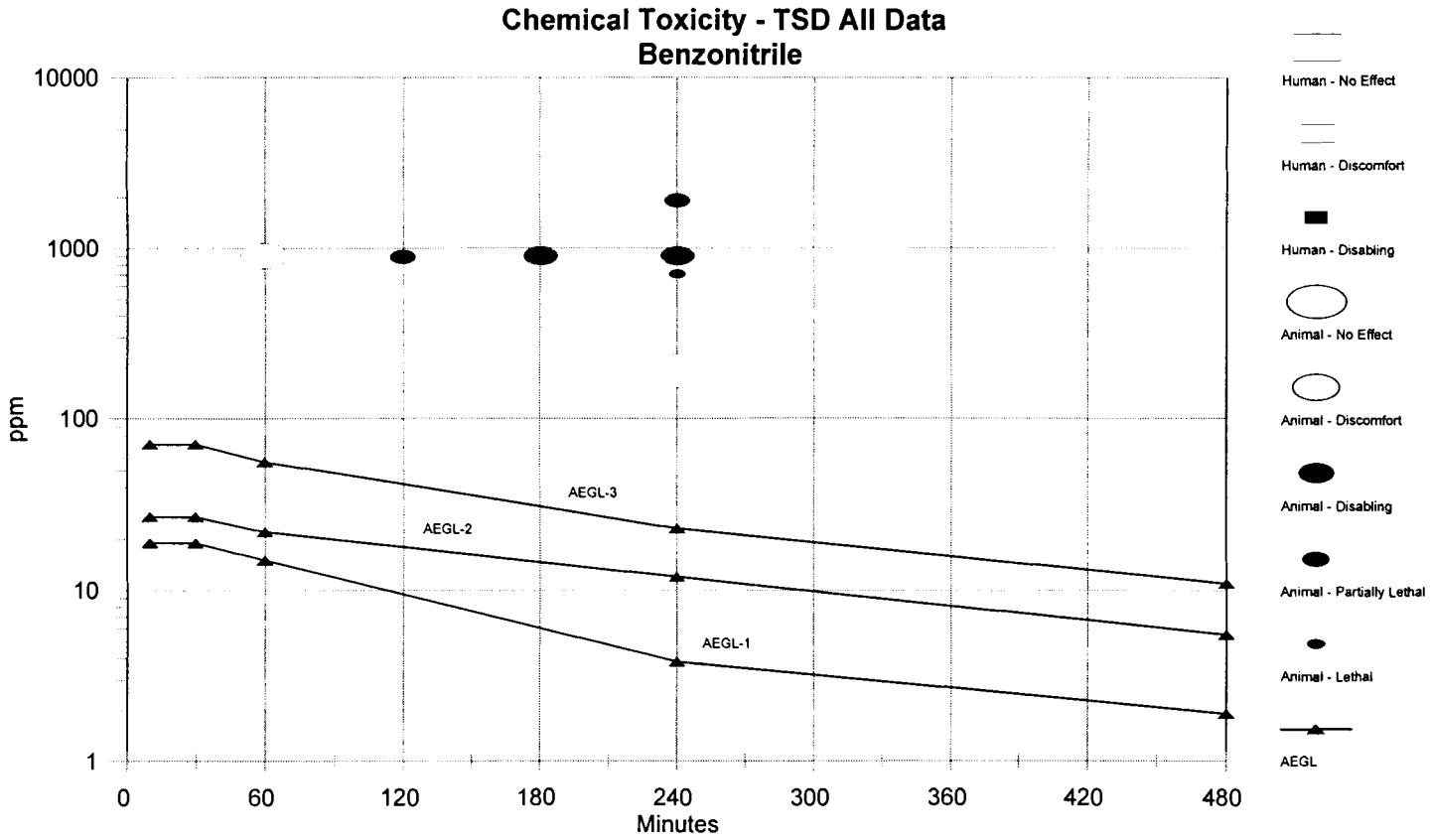
Rats exposed orally (0.6 g/kg, 0/4 deaths vs. 2.0 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Rabbits exposed dermally (0.9 g/kg, 0/4 deaths vs. 1.4 g/kg, 4/4 deaths) (Industrial Bio-Test, 1970).

Modifying Factor = 2 Endpoint where 1/10 mice died; Sparse data base and potential delayed hepatic effects, such as the hepatic congestion evidenced in mice

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR BENZONITRILE!

Summary of Proposed AEGL Values for Benzonitrile					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	19 ppm	19 ppm	15 ppm	3.8 ppm	2.0 ppm
AEGL-2	27 ppm	27 ppm	22 ppm	12 ppm	5.5 ppm
AEGL-3	71 ppm	71 ppm	56 ppm	23 ppm	11 ppm


Chemical Toxicity - TSD All Data
Benzonitrile
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL

Comparative Survey of Acute Inhalation Health Reference Values

George M. Woodall, PhD
Toxicologist – EPA/ORD/NCEA

Presented to SRA
December 9, 2003

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Categories of Acute Health Standards and Guideline Levels

- Occupational
  - Healthy worker population
  - Exposures for average workday/workweek and short-term peaks
- Emergency Response
  - General population – not necessarily the "most susceptible"
  - Rare, short-term exposures
- Public Health Protection
  - All susceptible individuals (generally)
  - More routine, potentially repeated exposures

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Acute Reference Value Definitions

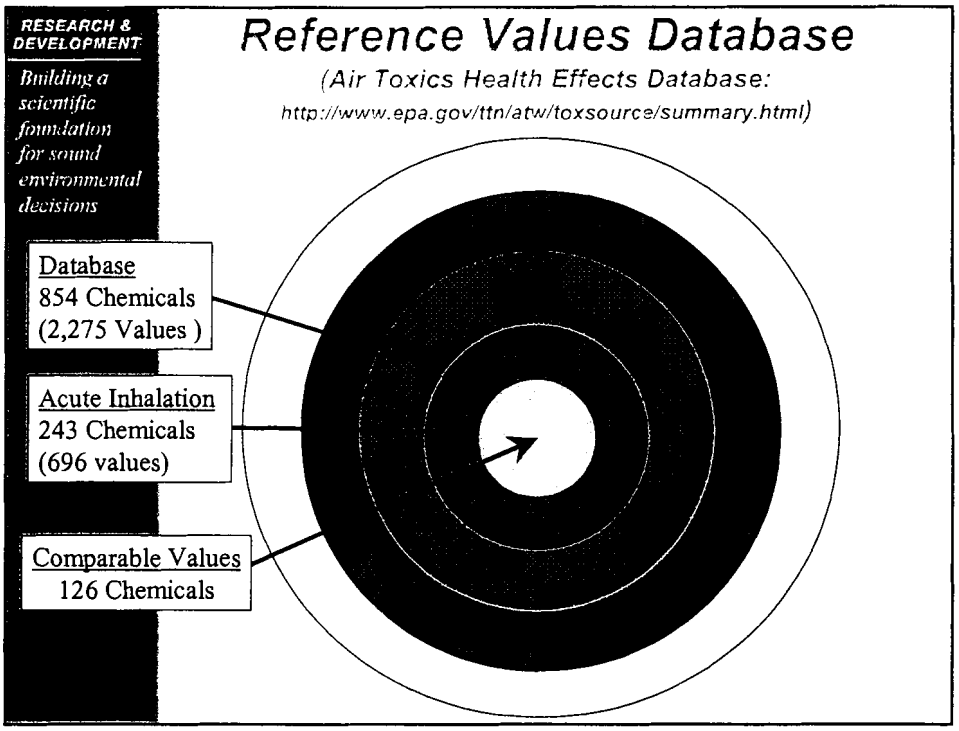
Reference Value	Organization	Legal Standing	Type Value	TWA (Yes/No)	Exposure Duration
PEL - Permissible Exposure Limit	OSHA	Standard	Occupational	Yes	8-hour
Ceiling	OSHA	Standard	Occupational	No	Up to10-minute
REL - Recommended Exposure Limit	NIOSH	Guideline	Occupational	Yes	8-hour
IDLH - Immediately Dangerous to Life and Health	NIOSH	Guideline	Occupational	No	Up to 30-minute
STEL - Short Term Exposure Limit	NIOSH	Guideline	Occupational	Yes	15-minute
TLV - Threshold Limit Value	ACGIH	Guideline	Occupational	Yes	8-hour
TLV-STEL - TLV Short Term Exposure Limit	ACGIH	Guideline	Occupational	Yes	15-minute
AEGL - Acute Exposure Guideline Level	NAC/ABGL & NAS/ABGL	Guideline	Emergency Response		10-minute, 30-minute, 1-hour, 4-hour, and 8-hour
ERPG - Emergency Response Planning Guideline	AIHA	Guideline	Emergency Response		1-hour
TEEL - Temporary Emergency Exposure Level	DOE	Guideline	Emergency Response		1-hour
ERG - Emergency Response Guidebook	DOT	Guideline	Emergency Response		Specialized application to chemicals in transportation accidents
MRL - Minimal Risk Level	ATSDR	Guideline	Public Health		1-14 days (acute); 15-364 days (intermediate); >365 days (chronic)
REL - Reference Exposure Level	OEHHA	Guideline	Public Health		1-8 hours
ARE - Acute Reference Exposure	EPA	Draft Guideline	Public Health		1-, 4-, 8-, and 24-hours

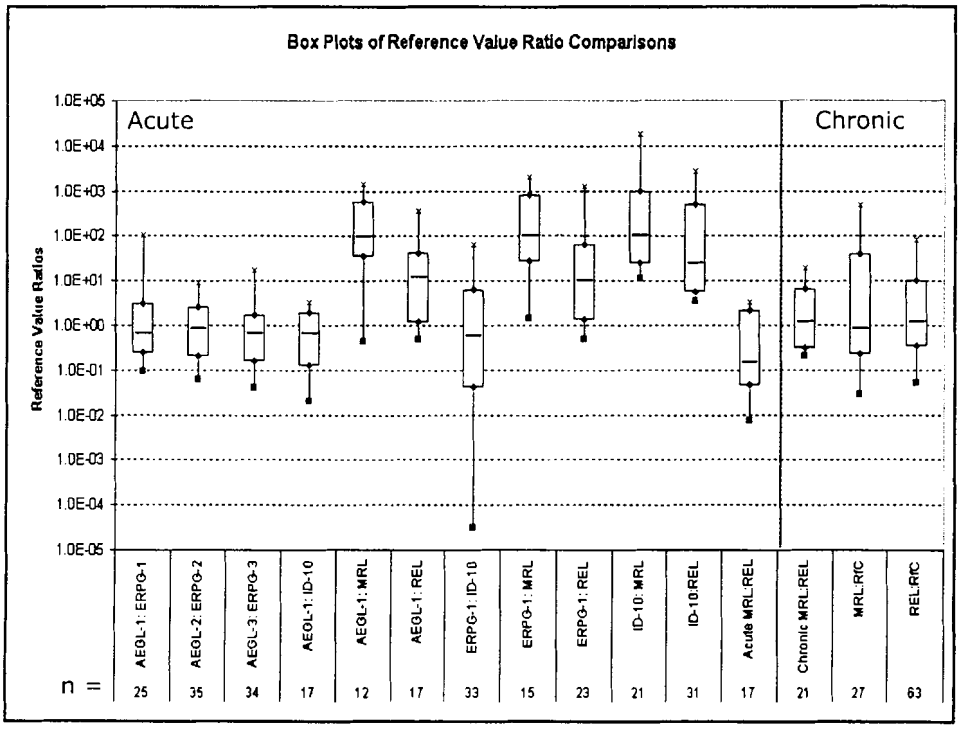
RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Purpose of Analysis: Residual Risk Support

- Characterize the Acute Reference Values for HAPS
  - Best value to use in individual Residual Risk assessments
- Understand the variability between values
  - Determine best course when critical Acute Reference Values are missing
- Three phases
  - ✓ Preliminary
  - ✓ Pilot
  - Full


RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions
Reference Values Database
(Air Toxics Health Effects Database:
http://www.epa.gov/ttn/atw/toxsource/summary.html)
Database
854 Chemicals
(2,275 Values)
Acute Inhalation
243 Chemicals
(696 values)
Comparable Values
126 Chemicals

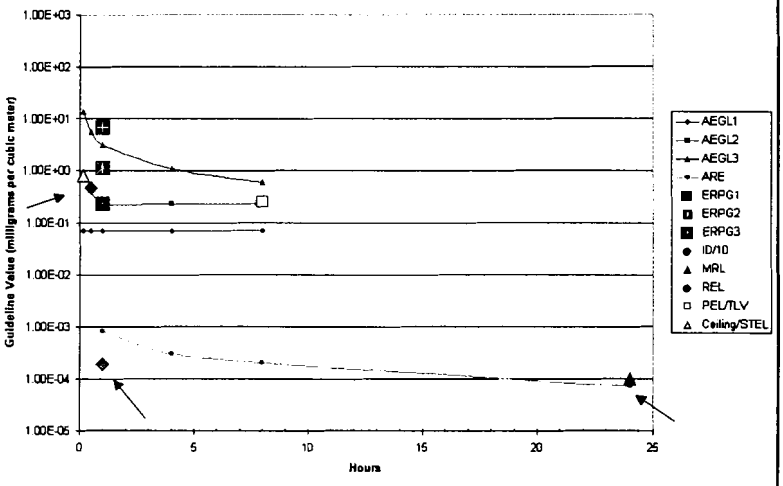

Box Plots of Reference Value Ratio Comparisons
Acute
Chronic
Reference Value Ratios
1.0E+05
1.0E+04
1.0E+03
1.0E+02
1.0E+01
1.0E+00
1.0E-01
1.0E-02
1.0E-03
1.0E-04
1.0E-05
AEGL-1: ERPG-1
AEGL-2: ERPG-2
AEGL-3: ERPG-3
AEGL-1: ID-10
AEGL-1: MRL
AEGL-1: REL
ERPG-1: ID-10
ERPG-1: MRL
ERPG-1: REL
ID-10: MRL
ID-10:REL
Acute MRL:REL
Chronic MRL:REL
MRL:RfC
REL:RfC
n =
25
35
34
17
12
17
33
15
23
21
31
17
21
27
63

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Pilot Study

Comparison of Values for Acrolein

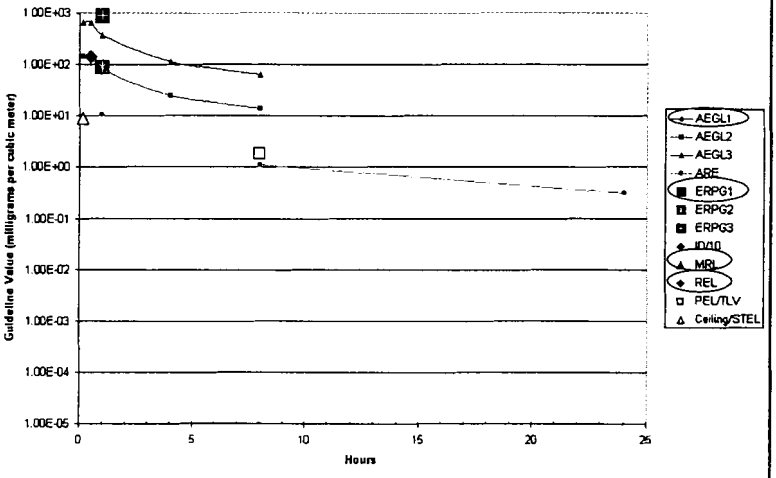


RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Pilot Study

Comparison of Values for Ethylene Oxide

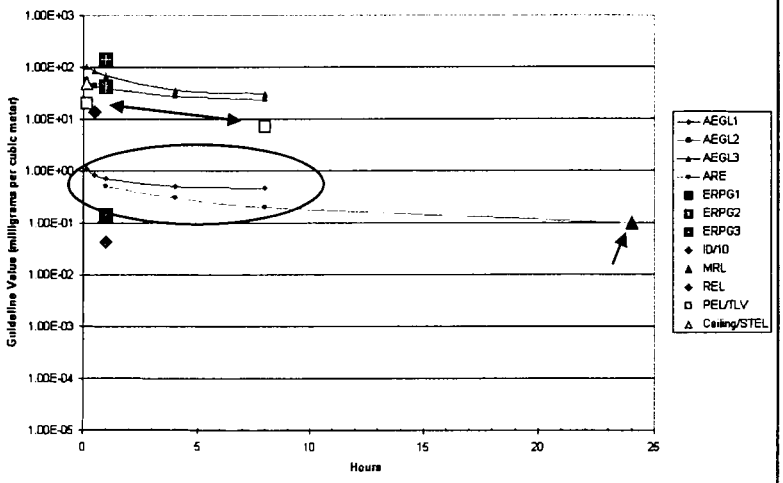


RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Pilot Study

Comparison of Values for Hydrogen Sulfide

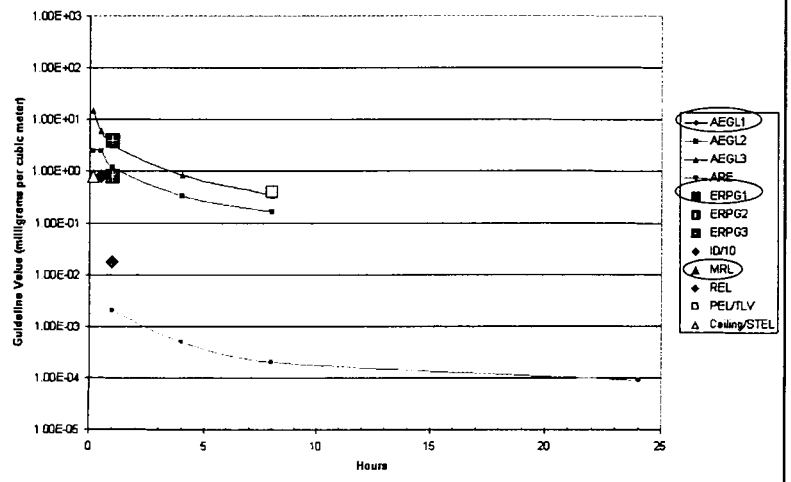


RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Pilot Study

Comparison of Values for Phosgene



RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Pilot Study - Conclusions

- Duration is critical for valid comparisons
- Not enough information was gathered to determine if other considerations (endpoint, target organ, etc.) will affect comparisons

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Full Analysis

- Add Duration data for AEGLs when making comparisons
- Add Occupational Reference Values
- Develop graphic templates for comparisons
- Add data "enhancements" in phases
  - Complete all data "enhancements" for some priority subset
  - Follow-up analysis and decide on whether to proceed to next phase.
  - If deemed useful, complete for all or most of chemicals and/or modify approach

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Comparison of Acute to Chronic Reference Values

- Determine which acute values may be more critical for Residual Risk Assessments
- Simple comparison (ratios) of acute to chronic values for single chemicals

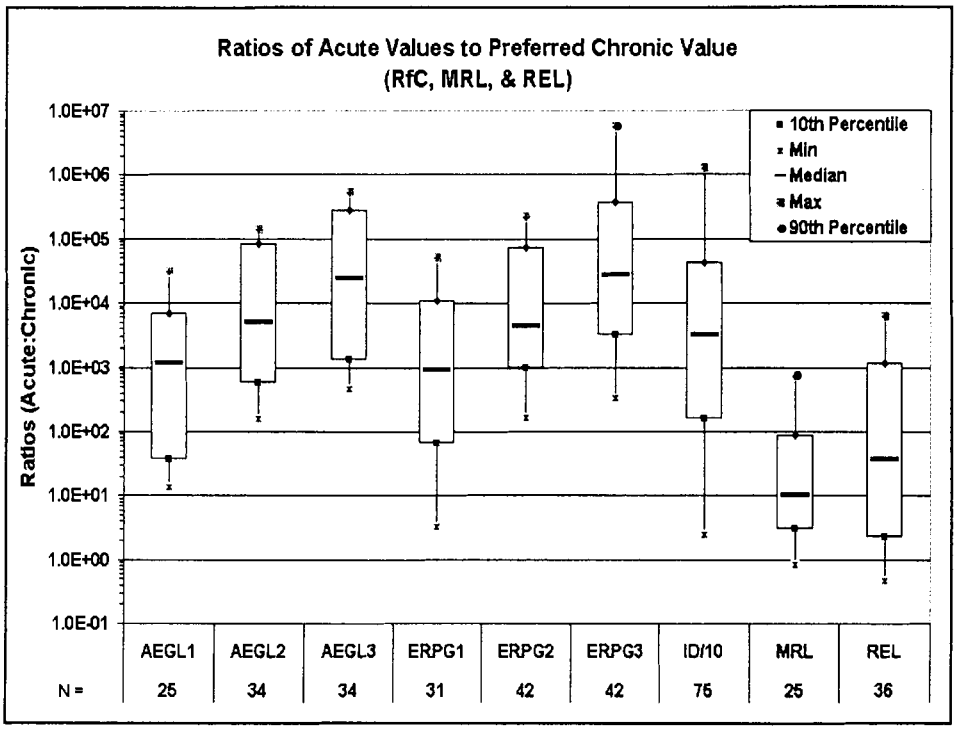
RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Table 3 – Ratio of Acute to Chronic Non-Cancer Inhalation Reference Values by HAP Chemical
(portion of full table showing three chemicals)

Acute Reference Values				
ID/10	9.00E+00	mg/cu m	4.50E+05	
Acute Reference Values				
AEGL1	1.24E+01	mg/cu m	1.78E+01	**
AEGL2	4.98E+02	mg/cu m	7.11E+02	*
AEGL3	1.49E+03	mg/cu m	2.13E+03	
ERPG1	3.11E+00	mg/cu m	4.45E+00	***
ERPG2	1.56E+02	mg/cu m	2.22E+02	*
ERPG3	1.56E+03	mg/cu m	2.22E+03	
ID/10	1.56E+02	mg/cu m	2.22E+02	*
REL	6.20E+00	mg/cu m	6.86E+00	***
Acute Reference Values				
AEGL1	7.55E+01	mg/cu m	1.89E+03	
AEGL2	3.52E+02	mg/cu m	8.81E+03	
AEGL3	1.07E+03	mg/cu m	2.67E+04	
ERPG1	1.26E+02	mg/cu m	3.15E+03	
ERPG2	6.29E+02	mg/cu m	1.57E+04	
ERPG3	4.72E+03	mg/cu m	1.18E+05	
ID/10	1.26E+02	mg/cu m	3.15E+03	
MRL	1.26E+00	mg/cu m	3.15E+01	**
REL	1.90E+00	mg/cu m	4.75E+01	**

*** <= 10; ** <= 100; * <= 1,000



RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Acute to Chronic Comparisons

- 92 chemicals had ratios calculated:
  - 25 had a lowest ratio value ≤10
  - 16 had a lowest ratio value > 10 and ≤100
  - 19 had a lowest ratio value > 100 and ≤1000
  - 32 had a lowest ratio value > 1000

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Summary

- Health Reference Values are developed for specific purposes and use outside those purposes should be done cautiously, if at all
- Comparisons between Health Reference Values
  - More valid within certain categories (occupational, emergency releases, public health protection) and
  - For comparable time frames
- Acute reference values for some chemicals may be more critical for residual risk analysis than their corresponding chronic values.

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

What Else is on the Horizon

EPA methodology for RfC-type acute values

- Methods available will include:
  - CatReg
  - BMD
  - NOAEL/LOAEL Approach
- Applies $C^n \times T^m$ time-course calculations where appropriate
- Other less-than-lifetime reference values are also under consideration
  - Short-term: 1-30 Days
  - Sub-chronic: 30 days to several years
- Draft documentation expected by 2005

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances

September 16-17, 2003

Final Meeting-30 Highlights

U.S. Department of Labor
200 Constitution Avenue, N.W., Rm 4437-B,C,D
Washington, DC 20210

INTRODUCTION

The draft NAC/AEGL-29 meeting highlights were reviewed. There were no corrections or comments, and a motion was made by Loren Koller and seconded by John Hinz to accept the meeting highlights as presented. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-29 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail.

Ernie Falke discussed highlights of the July COT AEGL Subcommittee meeting. The COT subcommittee was concerned that the AEGL-2 and AEGL-3 values were very close for phosphine (less than a factor of 2), and questioned whether there should be a specific minimal difference between AEGL tiers because of the needs of emergency planners. It was pointed out that AEGL tiers for other chemicals, such as aniline, hydrogen cyanide and phosgene were also close together. George Rusch pointed out that in all of these cases the closeness of values reflects the exposure-response data (very steep concentration-response curve). After some discussion, the NAC felt that this closeness of values was appropriate and should be retained; doing otherwise would not reflect the toxicity of the chemical. Therefore, a comment will be added to the phosphine TSD acknowledging the closeness of the AEGL-2 and AEGL-3 values and explaining the basis of this closeness. Regarding the Level of Odor Awareness (LOA), the COT requested that the LOA methodology be published, either as an RIVM document or in the Journal of Inhalation Toxicology. Hopefully, this publication will precede the publication of any TSD that includes an LOA. The COT also requested that the following issues be addressed when the SOP is updated: RD_{50} and its use in developing AEGLs, benchmark dose approach, rounding and time-scaling, holding irritation concentrations stable across time, PBPK issues, modifying factor use, and time scaling vs. constant values for solvents (Attachment 1).

Ernie Falke distributed proposed chemical lists for NAC- 32, 33, 34, and 35 (March-December, 2004) and asked NAC members to volunteer to be chemical manager for these priority chemicals (Attachment 2).

A revised draft of language to be added to the SOP regarding use of occupational studies, prepared by John Morawetz, was reviewed. A motion was made by George Alexeeff and seconded by Richard Niemier to accept the revised language for inclusion into the SOP as presented. The motion passed unanimously by a voice vote (Attachment 3).

The highlights of the NAC/AEGL-30 meeting are summarized below along with the Meeting Agenda (Attachment 4) and the Attendee List (Attachment 5). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-30 Agenda.

RESPONSES TO *FEDERAL REGISTER* COMMENTS ON THE PROPOSED AEGL VALUES

(A) Comments from the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for Phosphorus trichloride and Acetone cyanohydrin were received and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

PHOSPHORUS TRICHLORIDE

Comments were received from John Morawetz regarding supporting data for AEGL-1. Human data from an abstract by Sassi (1952) were used as supporting information for AEGL-1 values. After discussion, it was agreed that it would be best to remove the Sassi report as support for AEGL-1 values due to ambiguities in the study report. A motion to move the chemical from proposed to interim status was made by John Morawetz and seconded by David Belluck. The motion was approved unanimously by the NAC/AEGL (Appendix B).

ACETONE CYANOHYDRIN

Comments were received from John Morawetz and the Methacrylate Producers Association, Inc. Mr. Morawetz was concerned that descriptions of two occupational hydrogen cyanide studies (El Ghawabi et al., 1975, and Leeser, 1990) were in need of revision. The descriptions of these studies will be made consistent with the study descriptions in the hydrogen cyanide TSD. Mark Hamilton made a presentation on behalf of the Methacrylate Producers Association, explaining that hydrogen cyanide (HCN) is the principal hazard from acetone cyanohydrin (ACN) exposure. The Association's comments stated that ACN volatilizes rapidly and almost completely to HCN and that ACN itself is not detected during a release. Therefore, no separate AEGL values are needed for ACN. If separate values for ACN are derived, the Methacrylate Producers Association stated that there would be no justification for setting ACN values lower than HCN values. Peter Griem then responded to the comments (Attachment 6). After discussion, a motion was made by Ernest Falke and seconded by Richard Thomas to adopt HCN AEGL-2 and AEGL-3 values as AEGL-2 and AEGL-3 values for ACN; and to remove the MF of 2 from the ACN AEGL-1 values; and to raise the document to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix C). This approach used ACN data to develop AEGL-1 values that are very similar to the HCN AEGL-1 values. A footnote will also be

added stating that these are nominal values for ACH and actual exposure may include acetone, HCN, and ACN. The interim values are presented in the table below.

Summary of Interim AEGL Values for Acetone Cyanohydrin [ppm]						
Classification	**10-minutes**	**30-minutes**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	2.1	2.1	1.7	1.1	0.69	Red nasal discharge in rats
AEGL-2	17	10	7.1	3.5	2.5	HCN AEGL-2 values adopted as ACN AEGL-2 values
AEGL-3	27	21	15	8.6	6.6	HCN AEGL-3 values adopted as ACN AEGL-3 values

(B). No comments were received regarding the *Federal Register Notice* of May 28, 2003, on the proposed AEGL values for Fluorine, Jet Fuel, Monochloroacetic acid, and Phosphorus oxychloride. Therefore, these chemicals were elevated to Interim status as indicated below.

FLUORINE

No comments were received regarding the *Federal Register Notice* of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix D).

JET FUEL

No comments were received regarding the *Federal Register Notices* of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix E).

MONOCHLOROACETIC ACID

No comments were received regarding the *Federal Register Notices* of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix F).

PHOSPHORUS OXYCHLORIDE

No comments were received regarding the *Federal Register Notices* of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix G).

(C). Comments regarding the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for Bromine, Methyl ethyl ketone, Xylenes, and Ammonia were received and will be discussed at NAC-31 (December, 2003) due to the following reasons: Ammonia: The Fertilizer Institute requested, and received, a 60 day extension of the Public Comment Period; Bromine: extensive comments were very recently received; and Xylene and Methyl ethyl ketone are being evaluated to determine if PBPK modeling is feasible.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS

Phenol (CAS No. 108-95-2)

Chemical Manager: Robert Snyder
Staff Scientist: Peter Griem, FOBIG

Peter Griem discussed concerns expressed by the COT AEGL Subcommittee (Attachment 7). Major concerns were as follows: (1) All the AEGL values for phenol were too conservative and that the ERPG values were far more consistent with the phenol toxicologic profile; (2) Use of a NOAEL from a 2 week animal study as the basis of AEGL-1; (3) AEGL-2 values were derived as a fraction of the AEGL-3 values; and (4) Questionable validity of the AEGL-3 key study. After much discussion, a motion was made by George Rodgers and seconded by Richard Niemier to adopt revised AEGL-1 values of 8.3 ppm at all time points; AEGL-3 values of 200 ppm, 200 ppm, 160 ppm, 98 ppm, and 87 ppm for the 10-min, 30-min, 1-hr, 4-hr, and 8-hr time points, respectively; and AEGL-2 values of 1/3 the AEGL-3 values. (The rationale for this proposal is detailed in Attachment 7). The motion did not pass (YES:6: NO: 8; ABSTAIN: 2) (Appendix H). Further discussion of phenol was postponed until the December, 2003, meeting.

Carbon Monoxide (CAS No. 630-08-0)

Chemical Manager: George Rodgers
Staff Scientist: Peter Griem, FOBIG

Peter Griem discussed concerns expressed by the COT AEGL Subcommittee (Attachment 8). Major concerns were as follows: (1) AEGL-2 and AEGL-3 values for carbon monoxide were conservative; (2) Use of a 4% COHb as the basis of AEGL-2; and (3) Questionable validity of the AEGL-3 key studies. After discussion, NAC consensus was not to change the proposed AEGL values for carbon monoxide. Rather, a cover letter will be written stating that communications with cardiologists indicated that they could not correlate signs/symptoms to the COHb level of concern (AEGL-2). The justification for AEGL-3 values will be strengthened, perhaps by using NAAQs (National Ambient Air Quality Standards) documentation as support. It was also requested that NAC members with supporting information send these data to Peter Griem.

Acrylic Acid (CAS No. 79-10-7)

Chemical Manager: Ernest Falke
Staff Scientist: Peter Griem, FOBIG

Dr. James McLaughlin, Chairman of the Basic Acrylic Monomer Manufacturers, Inc. (BAMM), provided additional data and a letter (Attachment 9) regarding the COT AEGL Subcommittee's comments on the acrylic acid TSD to assure that all information was considered. The letter had not been distributed to the NAC prior to the meeting. BAMMs major concerns were as follows: (1) An AEGL-1 value of 1.5 ppm is too low because RD_{50} work suggests the irritation threshold to be at or above 6-8 ppm. The Renshaw data supports an AEGL-1 of 5-10 ppm and is consistent with international consensus; (2) AEGL-3 values are substantially too low and cannot be reconciled with current data, especially nose-only vapor exposures; and (3) LOA values are subject to abuse unless it is clearly stated that no health effects are implied.

Peter Griem discussed concerns expressed by the COT AEGL Subcommittee (Attachment 10). The COT AEGL Subcommittee's major concerns were as follows: (1) Use of a personal communication as the key study for AEGL-1; (2) Use of histological changes of the olfactory epithelium as the basis of AEGL-2; and (3) Use of an aerosol study instead of a vapor study and use of the MLE_{01} instead of BMC_{05} as the basis of AEGL-3. After much discussion, the AEGL-1 values were increased from 1.0 ppm at all time points to 1.5 ppm at all time points. Rationale for this approach is presented on page 8 of Attachment 10. AEGL-2 and AEGL-3 values were retained.

REVIEW OF CHEMICAL WITH ISSUES FROM PREVIOUS MEETINGS

Vinyl Chloride (CAS No. 75-01-4)

Chemical Manager: Robert Benson
Staff Scientist: Fritz Kalberlah, FOBIG

Bob Benson, Chemical Manager, provided a brief update on the changes to the VC TSD. These changes included revision in the description of an occupational study, revision to the calculations of cancer risk in the appendix, including an additional appendix describing additional assessment of cancer incidence from occupational exposure, and addition of a table with the cancer calculations to the Executive Summary. There have been no changes in the AEGL values previously approved by the Committee. As the cancer calculations do not require a formal vote of the committee, Bob proposed that the document (after editorial revisions) be submitted to the Federal Register and made available for public comment.

REVIEW of PRIORITY CHEMICALS

STYRENE
(CAS No. 100-42-5)

Chemical Manager: Loren Koller
Staff Scientist: Jens-Uwe Voss, Toxicological consultant, Germany

Jens-Uwe Voss presented an overview of the database and AEGL development for styrene (Attachment 11). Ursula Gundert-Remy then presented information on sensitive populations. Various models have suggested that P450 activity in infants is > 5-fold less than in adults; there fore an intraspecies UF of 3 may not be sufficient for a newborn.

The proposed AEGL-1 value was based on a NOAEL for irritation in humans of 20 ppm (Seeber et al., 2002). The TSD scientist suggested applying an intraspecies uncertainty factor of 1, as the value is considered sufficiently conservative because only minor irritation and headache were noted at 50 ppm. A motion was made by George Rodgers and seconded by Richard Niemier to accept an AEGL-1 value of 20 ppm for all time points because there is adaptation to the slight irritation that defines the AEGL-1. The motion passed (YES: 14; NO: 1; ABSTAIN: 1) (Appendix I). It was noted that utilizing the minor irritation and headache noted at 50 ppm and applying an intraspecies UF of 3, yields a supporting value of 17 ppm.

The proposed AEGL-2 was based on CNS effects in humans during and after exposure to 376 ppm for 1 hour (Stewart et al., 1968). The TSD scientist suggested applying an intraspecies UF of 3 because toxicokinetic data for humans indicate several-fold higher blood levels at heavy exercise, but high exercise cannot be maintained for hours and the endpoint is considered below the level of CNS depression that could impair escape. Time scaling using n=3 was proposed for the 10- and 30-minute values, and the 4- and 8-hour AEGL-2 values were set equal to the 1-hour value because toxicokinetic data for humans indicate very little or no increase at exposure times greater than 1 hour. Ursula Gundert-Remy reminded the group that P450 activity data suggest that infants under 1 year of age may be 5-fold more susceptible due to lower P450 activity, and questioned if the UF of 3 was sufficient. Susan Ripple then summarized information from a continuous styrene release from a train car near an assisted living facility. Ten nurses and fifteen responders, exposed to a 1.5 hour TWA of 490 ppm (range 425 to 529 ppm 15 min breathing zone samples), experienced headache, ocular and upper respiratory irritation, and nausea, while continuing work to evacuate residents. These data suggest that the proposed AEGL-2 values do not impair ability to escape. Susan will send this report to Paul Tobin. A motion was made by Bob Benson and seconded by Ernest Falke to accept the proposed AEGL-2 values of 230 ppm for 10-minutes, 160 ppm for 30-minutes, and 130 ppm for 1-, 4-, and 8-hours. The motion passed (YES: 13; NO: 3; ABSTAIN: 1) (Appendix I).

The proposed AEGL-3 was based on a 4-hour $BMDL_{05}$ of 3400 ppm in female rats (BASF, 1979). The TSD scientist suggested applying intraspecies and interspecies UFs of 3 each resulting in a total UF of 10. Time scaling using a chemical-specific, empirically derived n= 1.2

was proposed. Larry Gephart expressed concern over extrapolation from a 4-hour starting point to the 10-minute AEGL value. Concern was also expressed about extrapolation to 8-hours from the 4-hour starting point because toxicokinetic data for humans indicate very little or no increase at exposure times greater than 1 hour. A motion was made by Bob Snyder and seconded by Ernest Falke to accept the AEGL-3 values of 1900 ppm for 10- and 30-minutes, 1100 ppm for 1-hour, and 340 ppm 4-, and 8-hours. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (Appendix I).

The proposed LOA of 0.54 ppm was unanimously by a show of hands.

Summary of AEGL Values for Styrene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	NOAEL for irritation (Seeber et al., 2002)
AEGL–2	230 ppm 980 mg/m^3	160 ppm 680 mg/m^3	130 ppm 550 mg/m^3	130 ppm 550 mg/m^3	130 ppm 550 mg/m^3	CNS effects - human (Stewart et al. 1968)
AEGL–3	1900 ppm 8090 mg/m^3	1900 ppm 8090 mg/m^3	1100 ppm 4690 mg/m^3	340 ppm 1450 mg/m^3	340 ppm 1450 mg/m^3	$BMDL_{05}$ in female rats (BASF, 1979)

PROPANE
CAS Reg. No.74-98-6

Chemical Manager: Larry Gephart
Staff Scientist: P. J. M. Bos, RIVM, The Netherlands

The chemical review on propane was presented by Peter Bos (Attachment 12). The proposed AEGL-1 values were based on no effects in humans exposed to 10,000 propane for 10 minutes (Patty and Yant, 1929). An intraspecies UF of 1 was proposed because of the very steep concentration-response curve (for butane) implying little interindividual variability. Time scaling using n= 3 was proposed for extrapolation to 30-minutes and 1-hour, and it was proposed that the 1-hour value be adopted as both the 4- and 8-hour AEGL-1 values because steady-state is reached within 30 minutes. Proposed AEGL-1 values for propane were 10,000 ppm for 10-min, 6900 ppm for 30-min, and 5500 ppm for 1-, 4-, and 8-hours. It was noted that the AEGL-1 value is higher than10% of the lower explosive limit of propane in air (LEL = 2.3% (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

The proposed AEGL-2 values are based on a NOEL for cardiac sensitization in dogs at 50,000 ppm (Reinhardt et al., 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 1 was proposed because the dog is an optimized supersensitive model for humans. The value of 17,000 ppm was applied across all time points because cardiac sensitization is a concentration-related threshold effect. Because the AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3% (23,000

ppm)), the AEGL-2 values were not presented in the Table, but rather in a footnote. Safety considerations against hazard of explosion must be taken into account.

The proposed AEGL-3 values are based on a concentration causing no deaths in a cardiac sensitization study in dogs at 100,000 ppm (Reinhardt et al., 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 1 was proposed because the dog is an optimized supersensitive model for humans. The value of 33,000 ppm was applied across all time points because cardiac sensitization is a concentration-related threshold effect. Because the AEGL-3 value is higher than 100% of the lower explosive limit of propane in air (LEL = 2.3% (23,000 ppm)), the AEGL-3 values were not presented in the Table, but rather in a footnote. Safety considerations against hazard of explosion must be taken into account.

After some discussion, a motion was made by Loren Koller and seconded by John Hinz to accept the AEGL-1, AEGL-2, and AEGL-3 values as proposed, changing the footnote for the AEGL-3 values to indicate that the values are >100% of the Lower Explosive Limit (LEL) (not above 50% of the LEL). The motion passed (YES: 17; NO: 1; ABSTAIN: 1) (Appendix J).

Summary of AEGL Values for Propane

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	10,000 ppm* 5550 mg/m^3	6900 ppm* 3830 mg/m^3	5500 ppm* 3050 mg/m^3	5500 ppm* 3050 mg/m^3	5500 ppm* 3050 mg/m^3	NOEL in humans (Patty and Yant, 1929)
AEGL–2	See below¶	See below¶	See below¶	See below¶	See below¶	NOEL for cardiac sensitization in dogs (Reinhardt et al., 1971)
AEGL–3	See below‡	See below‡	See below‡	See below‡	See below‡	No mortality in dogs (Reinhardt et al., 1971)

*The AEGL-1 value is higher than10% of the lower explosive limit of propane in air (LEL = 2.3% (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

¶The AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3% (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated AEGL-2 values are held constant across all time periods: 17,000 ppm (9450 mg/m^3).

‡The AEGL-3 value is higher than 100% of the lower explosive limit of propane in air (LEL = 2.3% (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated AEGL-3 values are held constant across all time periods: 33,000 ppm (9450 mg/m^3).

Butane
CAS No. 106-97-8

Chemical Manager: Larry Gephart
Staff Scientist: P. J. M. Bos, RIVM, The Netherlands

The chemical review on butane was presented by Peter Bos (Attachment 13). The proposed AEGL-1 values were based on no effects in humans exposed to 10,000 butane for 10 minutes (Patty and Yant, 1929). An intraspecies UF of 1 was proposed because of the very steep concentration-response curve implying little interindividual variability. Time scaling using n= 3 was proposed for extrapolation to 30-minutes and 1-hour, and it was proposed that the 1-hour value be adopted as both the 4- and 8-hour AEGL-1 values because steady-state is reached within 30 minutes. Proposed AEGL-1 values for butane were 10,000 ppm for 10-min, 6900 ppm for 30-min, and 5500 ppm for 1-, 4-, and 8-hours. It was noted that, the AEGL-1 value is higher than 10% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

The proposed AEGL-2 values were based on a dazed appearance (but able to walk) in guinea pigs exposed to 50,000-56,000 ppm for 2 hours (Nuckolls, 1929). A total UF of 3 was proposed and considered sufficient because effects were due to butane and, thus, no large differences in kinetics would be expected and a higher UF would yield AEGL-2 values close to AEGL-1 values. Time scaling using n= 3 was proposed for extrapolation to 10- and 30-minutes and 1-hour, and it was proposed that the 2-hour point of departure value be adopted as both the 4- and 8-hour AEGL-2 values because steady-state is reached within 30 minutes. Proposed AEGL-2 values for butane were 38,200 ppm for 10-min, 26,500 ppm for 30-min, 21,000 ppm for 1-hour, and 16,700 ppm for 4- and 8-hours. Because the AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)), the AEGL-2 values were not presented in the Table, but rather in a footnote. Safety considerations against hazard of explosion must be taken into account.

The proposed AEGL-3 values were based on a calculated 2-hour LC_{01} in mice of 160,000 ppm (Shugaev, 1969). A total UF of 3 was proposed and considered sufficient because effects were due to butane and, thus, no large differences in kinetics would be expected, the steep concentration-response curve suggested small interindividual variability, and the most sensitive species was used. Time scaling using n= 3 was proposed for extrapolation to 10- and 30-minutes and 1-hour, and it was proposed that the 2-hour point of departure value be adopted as both the 4- and 8-hour AEGL-2 values because steady-state is reached within 30 minutes. Proposed AEGL-3 values for butane were 122,000 ppm for 10-min, 85,000 ppm for 30-min, 67,000 ppm for 1-hour, and 53,000 ppm for 4-, and 8-hours. Because the AEGL-3 value is higher than 100% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)), the AEGL-3 values were not presented in the Table, but rather in a footnote. Safety considerations against hazard of explosion must be taken into account.

After some discussion, a motion was made by John Hinz and seconded by George Rodgers to accept the AEGL-1 values as proposed, to accept AEGL-2 values of 25,000 ppm for 10-minutes and 17,000 ppm for 30-min, 1-, 4-, and 8-hours, and to accept AEGL-3 values of 76,000 ppm for 10-minutes and 53,000 ppm for 30-min, 1-, 4-, and 8-hours. The points of departure utilized for the AEGL-2 and AEGL-3 values are those described above. However, instead of scaling across time for the 30-min and 1-hr values, the 2-hr point of departures (with the UF of 3 applied) were held constant for the 30-min, 1-, 4-, and 8-hr time points, and time scaling using n=3 was applied to derive the 10-min AEGL-2 and AEGL-3 values because steady-state is reached within 30-

minutes, but not within 10-minutes. The motion passed (YES: 17; NO: 1; ABSTAIN: 1) (Appendix K).

Summary of AEGL Values for Butane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	10,000 ppm* 4200 mg/m^3	6900 ppm* 2900 mg/m^3	5500 ppm* 2300 mg/m^3	5500 ppm* 2300 mg/m^3	5500 ppm* 2300 mg/m^3	NOEL in humans (Patty and Yant, 1929)
AEGL–2	See below¶	See below¶	See below¶	See below¶	See below¶	dazed appearance (but able to walk) in guinea pigs (Nuckolls, 1929)
AEGL–3	See below‡	See below‡	See below‡	See below‡	See below‡	calculated 2-hour LC_{01} in mice (Shugaev, 1969)

*The AEGL-1 value is higher than 10% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.
¶The AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated AEGL-2 values are: 25,000 ppm (11,000 mg/m^3) for 10-min, and 17,000 ppm (7000 mg/m^3) for 30-min, and 1-, 4-, and 8-hours.
‡The AEGL-3 value is higher than 100% of the lower explosive limit of propane in air (LEL = 1.9% (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated AEGL-3 values are 76,000 ppm for 10-min, and 53,000 ppm (23,000 mg/m^3) for 30-min, and 1-, 4-, and 8-hours.

Dimethylsulfate
CAS No. 77-78-1

Staff Scientist: Susanne Gfatter, FOBIG
Chemical Manager: Bob Snyder

Susanne Gfatter described the data base for dimethylsulfate (Attachment 14). The proposed AEGL-1 was based on a 14-day repeated exposure study in rats (Frame et al. 1993; abstract publication). At 0.1 ppm for 6-hour, altered nasal cell proliferation without histopathological findings was observed. Evidence of only modest differences in toxicokinetics and toxicodynamics is available, therefore an interspecies factor of 3 is applied. The interspecies factor was further justified because the critical study used repeated exposure (Frame et al. 1993). No large differences in susceptibility between individuals are expected for nonspecific irritating effects, therefore an intraspecies factor of 3 is chosen. Default time scaling exponents of n=1 for extrapolation to 8-hr and n=3 when extrapolating to 30-min, 1-hr and 4-hr were proposed; the 10-min AEGL-1 was set equal to the 30-min value. Proposed AEGL-1 values were 0.023 ppm for 10- and 30-min, 0.018 ppm for 1-hour, 0.011 ppm for 4-hr, and 0.0075 ppm for 8-hr.

The proposed AEGL-2 values were based on asthma-like breathing sounds in rats, mice, and golden hamsters at exposed to 0.5 ppm for 6-hours (Schlögel,1972). Evidence of only modest differences in toxicokinetics and toxicodynamics is available, therefore an interspecies factor of 3

was proposed. No large differences in susceptibility between individuals are expected for nonspecific irritating effects, therefore an intraspecies factor of 3 was proposed. Default time scaling exponents of n=1 for extrapolation to 8-hr and n=3 when extrapolating to 30-min, 1-hr and 4-hr were proposed; the 10-min AEGL-2 was set equal to the 30-min value. Proposed AEGL-2 values were 0.11 ppm for 10- and 30-min, 0.091 ppm for 1-hour, 0.057 ppm for 4-hr, and 0.038 ppm for 8-hr.

The proposed AEGL-3 values were based a calculated 1-hr $BMCL_{05}$ of 5.8 ppm in guinea pigs (Hein, 1969). Evidence of only modest differences in toxicokinetics and toxicodynamics is available, therefore an interspecies factor of 3 was proposed. No large differences in susceptibility between individuals are expected for nonspecific irritating effects, therefore an intraspecies factor of 3 was proposed. Default time scaling exponents of n=1 for extrapolation to 4- and 8-hr and n=3 when extrapolating to 10- and 30-min were proposed. Proposed AEGL-3 values were 1.1 ppm for 10-min, 0.73 ppm for 30-min, 0.58 ppm for 1-hour, 0.15 ppm for 4-hr, and 0.073 ppm for 8-hr.

Discussion included the selection of the exponent, n, for scaling across time. LC_{50} values derived in rats of 64 ppm for an 1-hour duration (Hein, 1969) and of 32 ppm for a 4-hour exposure (Kennedy and Graepel, 1991) support the equation $C^2 \times t = k$. A similar time relationship was observed within mice, for which LC_{50} values of 98 ppm and 54 ppm were reported for an 1-hour and a 4-hour exposure, respectively (Hein, 1969; Molodkina et al. 1986). Discussion also involved selection of the key study for AEGL-3 derivation; it was suggested that the highest non-lethal concentration of 49 ppm (rats, 1-h exposure) be used for the derivation of the AEGL-3 values.

A motion was made by Loren Koller and Seconded by Ernest Falke to adopt AEGL-1 values of 0.035 ppm for 10- and 30-min, 0.024 ppm for 1-hr, 0.012 ppm for 4-hr and 0.0087 ppm for 8-hr; AEGL-2 values of 0.17 ppm for 10- and 30-min, 0.12 ppm for 1-hr, 0.061 ppm for 4-hr and 0.043 ppm for 8-hr; and AEGL-3 values of 12 ppm for 10- min, 6.9 ppm for 30-min, 4.9 ppm for 1-hr, 2.5 ppm for 4-hr and 1.7 ppm for 8-hr. These AEGL-1 and AGEL-2 values were based on the key studies/point of departure and UFs described in the proposals above; however, time scaling used n=2. These AEGL-3 values were based on the highest concentration causing no deaths in rats (49 ppm. 1hr), a total UF of 10, and time scaling using n = 2. The three AEGL tiers were balloted separately. The motion passed for AEGL-1 and AEGL-2 (YES: 19; NO: 0; ABSTAIN: 1) (Appendix L). The motion did not pass for AEGL-3 (YES: 6; NO: 8; ABSTAIN: 1) (Appendix L).
A motion was then made by Richard Thomas and seconded by Richard Niemier to adopt AEGL-3 values of 4.0 ppm for 10- min, 2.3 ppm for 30-min, 1.8 ppm for 1-hr, 0.82 ppm for 4-hr and 0.58 ppm for 8-hr. These AEGL-3 values were based on the highest concentration causing no deaths in rats (49 ppm for 1hr), a total UF of 30 (intra =3, inter =10 because the rat is not the most sensitive species), and time scaling using n = 2. The motion passed (YES: 19; NO: 0; ABSTAIN: 1) (Appendix L).

Summary of AEGL Values for Dimethylsulfate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.035 ppm 0.18 mg/m^3	0.035 ppm 0.18mg/m^3	0.024 ppm 0.12 mg/m^3	0.012 ppm 0.062 mg/m^3	0.0087 ppm 0.045 mg/m^3	nasal cell proliferation in rat (Frame et al., 1993)
AEGL–2	0.17 ppm 0.88 mg/m^3	0.17 ppm 0.88 mg/m^3	0.12 ppm 0.62 mg/m^3	0.061 ppm 0.32 mg/m^3	0.043 ppm 0.22 mg/m^3	breathing problems rat, mouse, hamster (Schlogel, 1972)
AEGL–3	4.0 ppm 21 mg/m^3	2.3 ppm 12 mg/m^3	1.6 ppm 8.3 mg/m^3	0.82 ppm 4.3 mg/m^3	0.58 ppm 3.0 mg/m^3	Concentration causing no death in rats (Hein, 1969)

ALIPHATIC NITRILES

Acetonitrile (CAS No. 75-05-8)
Isobutyronitrile (CAS No. 78-82-0)
Propionitrile (Cas No. 107-12-0)
Chloroacetonitrile (Cas No. 107-14-2)
Malononitrile (Cas No. 109-77-3)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rodgers

Cheryl Bast presented an overview of the five nitrile compounds addressed in the TSD (Attachment 15). The aliphatic nitriles metabolically liberate cyanide via cytochrome P450 mediated hydroxylation on the carbon alpha to the cyano group and the toxicity of these nitriles is due to cyanide. The relative toxicity of the nitriles is due to the rate of cyanide liberation; generally, the nitriles that are metabolized most quickly or easily at the carbon atom alpha to the cyano group (α-carbon) are more toxic than nitriles metabolized more slowly at the α-carbon.

Acetonitrile (CAS No. 75-05-8)

The proposed AEGL-1 was based on slight chest tightness and cooling sensation in the lungs noted by one of three human male volunteers exposed to 40 ppm acetonitrile for 4 hours (Pozzani et al., 1959). No intraspecies uncertainty factor was applied because the mild effects are considered to have occurred in a sensitive subject since no symptoms were reported by two other subjects exposed to this same regimen and no effects were noted at 80 ppm for 4 hours by these same two subjects. The 40 ppm concentration was held constant across all time points because no human data exist for periods of less than 4-hours; thus, time-scaling to shorter durations could yield values eliciting symptoms above those defined by AEGL-1.

The proposed AEGL-2 was based on slight pulmonary congestion or hemorrhage in rats exposed to 4000 ppm acetonitrile for 4 hours (Pozzani et al., 1959). An uncertainty factor of 10 was used to extrapolate from animals to humans because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great and AEGL-2 values derived with a total default uncertainty factor would yield values inconsistent with available human data. For scaling the AEGL-2 values for acetonitrile across time, the empirically-derived chemical-specific value of 2.5 (derived from rat lethality data ranging from 15 minutes to 8 hours exposure duration), was used as the exponent, *n*. The 30-minute AEGL-2 was also adopted as the 10-minute value due to the added uncertainty of extrapolating from a 4-hour time point to 10-minutes. Proposed AEGL-2 values were 310 ppm for 10- and 30-min, 230 ppm for 1 hour, 130 ppm for 4 hours, and 100 ppm for 8-hours.

The proposed AEGL-3 was based on a calculated 4-hour rat LC_{01} of 8421 ppm (Monsanto, 1986) . An uncertainty factor of 10 was used to extrapolate from animals to humans because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great, and AEGL-3 values derived with a total default uncertainty factor would be inconsistent with the total database (For scaling the AEGL values for acetonitrile across time, the empirically-derived chemical-specific value of 2.5 (derived from rat lethality data ranging from 15 minutes to 8 hours exposure duration), was used as the exponent, n. The 30-minute AEGL-3 was also adopted as the 10-minute value due to the added uncertainty of extrapolating from a 4-hour time point to 10-minutes. Proposed AEGL-3 values were 650 ppm for 10- and 30-min, 490 ppm for 1 hour, 280 ppm for 4 hours, and 210 ppm for 8-hours.

A motion was made by George Rodgers and seconded by John Hinz to accept the AEGL-values as presented. The AEGL-1, -2, and -3 values were polled separately. The motion did not pass for AEGL-1 (YES: 7; NO: 10; ABSTAIN: 1) (Appendix M). The motion passed for AEGL-2 (YES: 16; NO: 2; ABSTAIN: 2) (Appendix M), and AEGL-3 (YES: 17; NO: 2; ABSTAIN: 1) (Appendix M).

Concern was expressed about the sparse data set for AEGL-1. A motion was made by Bob Benson and seconded by John Morawetz to apply a modifying factor of 3 to the proposed AEGL-1 values to account for the sparse data set, yielding an AEGL-1 value of 13 ppm for all time points,. The motion passed (YES: 19; NO: 1; ABSTAIN: 0) (Appendix M).

Summary of AEGL Values For Acetonitrile						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**

AEGL-1	13 ppm 22 mg/m^3	13 ppm 22 mg/m^3	13 ppm 22 mg/m^3	13 ppm 22 mg/m^3	13 ppm 22 mg/m^3	Slight chest tightness and cooling sensation in lung (1/3 human volunteers) (Pozzani et al., 1959)
AEGL-2	310 ppm (520 mg/m^3)	310 ppm (520 mg/m^3)	230 ppm (390 mg/m^3)	130 ppm (218 mg/m^3)	100 ppm (168 mg/m^3)	Slight pulmonary congestion and hemorrhage in rats (Pozzani et al., 1959)
AEGL-3	650 ppm 1092 mg/m^3	650 ppm 1092 mg/m^3	490 ppm 820 mg/m^3	280 ppm 470 mg/m^3	213 ppm 360 mg/m^3	Calculated LC_{01} in the rat after a 4-hour exposure (Monsanto, 1986)

Isobutyronitrile (CAS No. 78-82-0)

Data were insufficient for derivation of AEGL-1 values for isobutyronitrile. The proposed AEGL-2 was based on a no-effect-level for maternal and fetal toxicity from a developmental toxicity study in rats (100 ppm, 6 hour/day, days 6-20 of gestation) (Saillenfait et al., 1993). An uncertainty factor of 3 was applied to account for sensitive individuals because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN, but the magnitude of these differences does not appear to be great. An interspecies uncertainty factor of 3 was also applied because use of the full uncertainty factor of 10, would yield AEGL-2 values that are not consistent with the total data set. An *n* of 3 was applied to extrapolate to the 10-minute, 30-minute, 1-hour, and 4-hour time periods, and an *n* of 1 was applied to extrapolate to the 8-hour time period, to provide AEGL values that would be protective of human health. Proposed AEGL-2 values were 33 ppm for 10-min, 23 ppm for 30-min, 18 ppm for 1 hour, 11 ppm for 4 hours, and 7.5 ppm for 8-hours.

The proposed AEGL-3 was based on a calculated 1-hour LC_{01} of 677 ppm in rats (Eastman Kodak Co., 1986a). An uncertainty factor of 3 was applied to account for sensitive individuals because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN, but the magnitude of these differences does not appear to be great. An interspecies uncertainty factor of 3 was also applied because use of the full uncertainty factor of 10, would yield AEGL-3 values that are not consistent with the total data set. An *n* of 3 was applied to extrapolate to the 10- and 30-minute time periods, and an *n* of 1was applied to extrapolate to the 4- and 8-hour time periods. were 120 ppm for 10-min, 85 ppm for 30-min, 68 ppm for 1 hour, 17 ppm for 4 hours, and 8.5 ppm for 8-hours.

After discussion, a motion was made by Ernest Falke and seconded by John Hinz to accept the AEGL-2, and -3 values as presented and "NR" for AEGL-1. The motion passed (YES: 15; NO: 3; ABSTAIN: 0) (Appendix N), and AEGL-3 (YES: 17; NO: 2; ABSTAIN: 1).

Summary of AEGL Values for Isobutyronitrile						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR*	NR	NR	NR	NR	Insufficient data to derive AEGL-1 values
AEGL-2	33 ppm 93 mg/m^3	23 ppm 65 mg/m^3	18 ppm 51 mg/m^3	11 ppm 31 mg/m^3	7.5 ppm 21 mg/m^3	No-effect-level in rats (Saillenfait et al., 1993)
AEGL-3	123 ppm 350 mg/m^3	85 ppm 240 mg/m^3	68 ppm 190mg/m^3	17 ppm 48 mg/m^3	8.5 ppm 24 mg/m^3	Calculated 1-hr LC_{01} in rats (Eastman Kodak, 1986a)

NR: Not Recommended.

Propionitrile (Cas No. 107-12-0)

Chemical-specific data are insufficient for the derivation of AEGL-1 values for propionitrile. Appropriate i.p. toxicity data are available for both acetonitrile and propionitrile; thus, it was proposed to derive AEGL-1 values for proprionitrile by analogy to acetonitrile AEGL-1 values. Mouse i.p. LD_{50} data suggest that propionitrile is approximately 21 times more toxic than acetonitrile. Therefore, the acetonitrile AEGL-1 values were divided by 21 to approximate AEGL-1 values for propionitrile. A modifying factor of 2 was also applied because the data suggesting that propionitrile is 21 times more toxic than acetonitrile are very limited, and thus, the value cannot be predicted with great precision. The proposed AEGL-1 value was 4.3 ppm at all time points.

The proposed AEGL-2 was based on headache, nausea, dizziness, vomiting, confusion, and disorientation in a 34-year-old male worker exposed to approximately 34 ppm propionitrile for 2 hours (Scolnick et al., 1993). An uncertainty factor of 3 was applied to account for sensitive individuals because human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods. The 30-minute AEGL-2 value was also adopted as the 10-minute value due to the fact that reliable data are limited to durations $\geq$2 hours, and it is considered inappropriate to extrapolate back to 10-minutes. Proposed AEGL-2 values were 18 ppm for 10- and 30-min, 14 ppm for 1 hour, 5.7 ppm for 4 hours, and 2.8 ppm for 8-hours.

The proposed AEGL-3 was based on the highest concentration (690 ppm) causing no mortality in rats exposed to propionitrile for four hours (Younger Labs, 1978). An interspecies uncertainty factor of 10 was applied because the rat is not the most sensitive species. An uncertainty factor of 3 was applied to account for sensitive individuals. An *n* of 3 was applied to extrapolate to the 30-minute and 1-hour time periods, and an *n* of 1 was applied to extrapolate to the 8-hour time period. The 30-minute AEGL-3 value was also adopted as the 10-minute value due to the fact that the values are derived from a 4 hour exposure, and it is considered

inappropriate to extrapolate back to 10-minutes. Proposed AEGL-3 values were 46 ppm for 10- and 30-min, 37 ppm for 1 hour, 23 ppm for 4 hours, and 12 ppm for 8-hours.

Discussion centered around the appropriateness of deriving AEGL-1 values for propionitrile by analogy to acetonitrile utilizing i.p. data. The NAC felt that this approach may be valid for effects defined by AEGL-2 or AEGL-3, but not effects defined by AEGL-1. Concern was also expressed that the data set for AEGL-2 is limited (the human accidental exposure included only 2 workers) and that perhaps a modifying factor for a sparse data base is appropriate. Ursula Gundert-Remy expressed concern that the proposed AEGL-3 values were very close to the human accidental exposure of 34 ppm for 7 hours that would have likely resulted in death had medical intervention not been obtained.

A motion was made by John Morawetz and seconded by Bob Benson to not recommend AEGL-1 values for propionitrile and to apply a modifying factor of 2 to the proposed AEGL-2 values to account for the sparse data set, yielding AEGL-2 values of 9.0 ppm for 10- and 30-min, 7.0 ppm for 1-hr, 2.9 ppm for 4-hr, and 1.4 ppm The AEGL-1 motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix O). The AEGL-2 motion passed (YES: 16; NO: 1; ABSTAIN: 0) (Appendix O). A motion was then made by Bob Benson and seconded by George Rodgers to accept AEGL-3 values as proposed. The AEGL-3 motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix O).

Summary of AEGL Values for Propionitrile

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	9.0 ppm 20 mg/m^3	9.0 ppm 20 mg/m^3	7.0 ppm 16 mg/m^3	2.9 ppm 6.5 mg/m^3	1.4 ppm 3.2 mg/m^3	Headache, nausea, vomiting, dizziness, confusion in a human subject (Scolnick et al., 1993)
AEGL-3 (Lethal)	46 ppm 100 mg/m^3	46 ppm 100 mg/m^3	37 ppm 83 mg/m^3	23 ppm 52 mg/m^3	12 ppm 7 mg/m^3	Highest concentration causing no death in rats (Younger Labs, 1978)

NR: Not Recommended

Chloroacetonitrile (Cas No. 107-14-2)

Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for chloroacetonitrile. In the absence of relevant chemical-specific data for chloroacetonitrile, it was proposed that a modification of the AEGL values for acetonitrile be utilized to derive AEGL-values for chloroacetonitrile. Mouse i.p. LD_{50} data suggest that chloroacetonitrile is approximately 5.2 times more toxic than acetonitrile. Therefore, the acetonitrile values were divided by 5.2 to approximate AEGL values for chloroacetonitrile. In the absence of inhalation data, the i.p. route was considered the most appropriate for approximating

inhalation toxicity values because both routes involve entry into the organism through a semipermeable membrane (peritoneal membrane and alveolar membrane) before diffusion into the blood. Furthermore, the magnitude and rate of effect (in descending order) for the different routes of administration are: intravenous, inhalation, intra peritoneal, subcutaneous, intramuscular, intradermal, oral, and topical (Klaassen, 1986).

During discussion, it was pointed out that molar equivalents must be used (not mg/kg comparisons) when determining relative toxicities from i.p. lethality data. On a molar basis, chloroacetonitrile is approximately 10 times more toxic than acetonitrile. A motion was made by Bob Benson and seconded by Richard Niemier to not recommend AEGL-1 values, to divide the acetonitrile AEGL-2 values by 2 to obtain AEGL-2 values for chloroacetonitrile (31 ppm for 10- and 30-min, 23 ppm for 1-hr, 13 ppm for 4-hr, and 10 ppm for 8-hr ppm), and to divide the acetonitrile AEGL-3 values by 10 to obtain AEGL-3 values for chloroacetonitrile (65 ppm for 10- and 30-min, 49 ppm for 1-hr, 28 ppm for 4-hr, and 21 ppm for 8-hr ppm). The motion passed (YES: 12; NO: 1; ABSTAIN: 3) (Appendix P).

Summary of AEGL Values for Chloroacetonitrile						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	
AEGL-2	31 ppm 52 mg/m^3	31 ppm 52 mg/m^3	23 ppm 39mg/m^3	13 ppm 22 mg/m^3	10 ppm 17 mg/m^3	Derived by analogy to acetonitrile AEGL-2 values
AEGL-3	65 ppm 110 mg/m^3	65 ppm 110 mg/m^3	49 ppm 82 mg/m^3	28 ppm 47 mg/m^3	21 ppm 36 mg/m^3	Derived by analogy to acetonitrile AEGL-3 values

NR: Not Recommended

Malononitrile (Cas No. 109-77-3)

Chemical-specific data were insufficient for the derivation of AEGL-1, AEGL-2, or AEGL-3 values for malononitrile. In the absence of relevant chemical-specific data for malononitrile, it was proposed that a modification of the AEGL values for acetonitrile be utilized to derive AEGL-values for chloroacetonitrile. Mouse i.p. LD_{50} data suggest that chloroacetonitrile is approximately 65 times more toxic than acetonitrile on a molar basis.

A motion was made by Bob Benson and seconded by Ernest Falke to not recommend AEGL-1 values, to divide the acetonitrile AEGL-2 values by 65 to obtain AEGL-2 values for malononitrile (4.8 ppm for 10- and 30-min, 3.5ppm for 1-hr, 2.0 ppm for 4-hr, and 1.5 ppm for 8-hr ppm), and to divide the acetonitrile AEGL-3 values by 65 to obtain AEGL-3 values for malononitrile (10 ppm for 10- and 30-min, 7.5 ppm for 1-hr, 4.3 ppm for 4-hr, and 3.2 ppm for 8-hr ppm). The motion passed (YES: 15; NO: 0; ABSTAIN: 0) (Appendix Q).

Summary of AEGL Values for Malononitrile						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	4.8 ppm 8.0 mg/m^3	4.8 ppm 8.0 mg/m^3	3.5 ppm 6.0 mg/m^3	2.0 ppm 3.4 mg/m^3	1.5 ppm 2.6 mg/m^3	Derived by analogy to acetonitrile AEGL-2 values
AEGL-3 (Lethal)	10 ppm 17 mg/m^3	10 ppm 17 mg/m^3	7.5 ppm 13 mg/m^3	4.3 ppm 7.2 mg/m^3	3.2 ppm 5.5 mg/m^3	Derived by analogy to acetonitrile AEGL-3 values

Administrative Matters

The site and time of the next meeting, NAC/AEGL-31, will be December 10-12, 2003 in San Antonio, Texas.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Robert Young, Oak Ridge National Laboratory, with input from the respective chemical managers, authors, and other contributors.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.
Attachment 1. Highlights of the COT/AEGL Subcommittee Meeting
Attachment 2. List of chemicals to be considered at the NAC-32, 33, 34, and 35
Attachment 3. Proposal for Evaluation of Occupational Monitoring Studies for inclusion in the SOP
Attachment 4. NAC/AEGL-30 Meeting Agenda
Attachment 5. NAC/AEGL-30 Attendee List
Attachment 6. Response to Federal Register comments for acetone cyanohydrin
Attachment 7. Response to COT subcommittee comments for phenol
Attachment 8. Response to COT subcommittee comments for carbon monoxide
Attachment 9. BAMM comments on acrylic acid
Attachment 10. Response to COT subcommittee comments for acrylic acid
Attachment 11. Data Analysis of styrene
Attachment 12. Data Analysis of propane
Attachment 13. Data Analysis of butane
Attachment 14. Data Analysis of dimethyl sulfate
Attachment 15. Data Analysis of aliphatic nitriles

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-29
Appendix B. Ballot for phosphorus trichloride
Appendix C. Ballot for acetone cyanohydrin
Appendix D. Ballot for fluorine
Appendix E. Ballot for jet fuel
Appendix F. Ballot for monochloroacetic acid
Appendix G. Ballot for phosphorus oxychloride
Appendix H. Ballot for phenol
Appendix I. Ballot for styrene
Appendix J. Ballot for propane
Appendix K. Ballot for butane
Appendix L. Ballot for dimethyl sulfate
Appendix M. Ballot for acetonitrile
Appendix N. Ballot for isobutyronitrile
Appendix O. Ballot for propionitrile
Appendix P. Ballot for chloroacetonitrile
Appendix Q. Ballot for malononitrile

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: AMMONIA (RAISE TO INTERIM + CHANGE AEGL-1 25→30ppm) **CAS Reg. No.:**

Chemical Manager: LARRY GEPHART **Staff Scientist:** KOWETHA DAVIDSON

NAC Member	AEGL1	AEGL2	AEGL3	~~LOA~~ *	NAC Member	AEGL1	AEGL 2	AEGL3	~~LOA~~ *
George Alexeeff	Y			Y	Nancy Kim	Y			Y
Steven Barbee	Y			Y	Loren Koller	P			Y
Lynn Beasley	Y			Y	Glenn Leach	A			A
Robert Benson	P			Y	Mark McClanahan	A			A
Jonathan Borak	Y			A	John Morawetz	Y			N
William Bress	Y			Y	Richard Niemeier	Y			Y
George Cushmac	Y			Y	Marinelle Payton	A			A
Ernest Falke	Y			Y	Zarena Post	A			A
Larry Gephart	A			A	George Rodgers	Y			Y
John Hinz	P			Y	George Rusch, Chair	Y			Y
Jim Holler	Y			Y	Robert Snyder	A			A
Thomas Hornshaw	Y			Y	Thomas Sobotka	A			A
					Richard Thomas	Y			Y
					TALLY	15/15			16/18

5 Mid

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1 30	30, ( )	30, ( )	30, ( )	30, ( )	30, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
~~LOA~~ RAISE TO INTERIM					

AEGL 1 Motion by: KIM **Second by:** ~~MORGAN~~ HORNSHAW

AEGL 2 Motion by: _____ **Second by:** _____

AEGL 3 Motion by: _____ **Second by:** _____

Elevate to Interim! Falke RODGERS * RAISE TO INTERIM

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/11/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: XYLENES **CAS Reg. No.:**

Chemical Manager: RICHARD THOMAS **Staff Scientist:** CLAUDIA TROXEL

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff		A	A		Nancy Kim		Y	P	
Steven Barbee		Y	Y		Loren Koller		Y	P	
Lynn Beasley		Y	Y		Glenn Leach				
Robert Benson		Y	Y		Mark McClanahan				
Jonathan Borak		A	A		John Morawetz		N	P	
William Bress		Y	Y		Richard Niemeier		Y	Y	
George Cushmac		Y	Y		Marinelle Payton				
Ernest Falke		Y	Y		Zarena Post				
Larry Gephart		A	A		George Rodgers		P	Y	
John Hinz		Y	Y		George Rusch, Chair		Y	Y	
Jim Holler		Y	Y		Robert Snyder				
Thomas Hornshaw		Y	Y		Thomas Sobotka				
					Richard Thomas		Y	Y	
					TALLY		14/14	13/13	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	1100,( )	600,( )	400,( )	400,( )	400,( )
AEGL 3	3300,( )	1700,( )	1100,( )	1100,( )	1100,( )
LOA					

AEGL 1 Motion by: _____ **Second by:** _____

AEGL 2 Motion by: Falke **Second by:** Hinz

AEGL 3 Motion by: Benson **Second by:** Falke

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/12/03

Appendix D

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: METHYL ETHYL KETONE **CAS Reg. No.:** 78-93-3
Elevate to Interim

Chemical Manager: BILL BRESS **Staff Scientist:** SYLVIA TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	N	P	P	
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	P	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Larry Gephart	A	A	A	
John Hinz	N	Y	Y	
Jim Holler	N	Y	Y	
Thomas Hornshaw	P	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Loren Koller	Y	Y	Y	
Glenn Leach	A	A	A	
Mark McClanahan	A	A	A	
John Morawetz	Y	P	Y	
Richard Niemeier	P	P	Y	
Marinelle Payton	A	A	A	
Zarena Post	A	A	A	
George Rodgers	P	P	Y	
George Rusch, Chair	P	Y	Y	
Robert Snyder	A	A	A	
Thomas Sobotka	A	A	A	
Richard Thomas	Y	Y	Y	
TALLY	9/12	13/13		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
* AEGL 1	200, ( )	200, ( )	200, ( )	200, ( )	200, ( )
AEGL 2 **	4900, ( ) **	3400, ( ) **	2200, ( )	1700, ( )	1700, ( )
AEGL 3 **	10000, ( ) **	10,006, ( ) **	4000, ( ) **	2500, ( ) **	2500, ( )
LOA					

* Revise to 200 ppm from 100 ppm based on new study.
** > 1/10 LEL (LEL = 18,000 ppm)

AEGL 1 **Motion by:** Koller **Second by:** Falke

AEGL 2 **Motion by:** Barbee **Second by:** Hinz

AEGL 3 **Motion by:** Koller **Second by:** Hinz

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/11/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: ACRYLIC ACID (DISCREPANCY WITH VALUES FOR AEGL-2 = REVOTE) **CAS Reg. No.:**

Chemical Manager: Ernie Falke **Staff Scientist:** Peter Greim

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff		Y			Nancy Kim		Y		
Steven Barbee		Y			Loren Koller		Y		
Lynn Beasley		Y			Glenn Leach		A		
Robert Benson		Y			~~Mark McClanahan~~				
Jonathan Borak		Y			John Morawetz		Y		
William Bress		Y			Richard Niemeier		Y		
George Cushmac		Y			Marinelle Payton		A		
Ernest Falke		Y			~~Zarena Post~~		A		
Larry Gephart	A	A			George Rodgers		Y		
John Hinz		A			George Rusch, Chair		Y		
Jim Holler		Y			Robert Snyder		A		
Thomas Hornshaw		Y			~~Thomas Sobotka~~				
					Richard Thomas		Y		
					TALLY		17/17		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	68,( )	68,( )	46,( )	21,( )	14,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					

* 3 Hr 75ppm is point of departure (monkey/rat) Rewording

AEGL 1 **Motion by:** _____ **Second by:** _____

AEGL 2 **Motion by:** * B. Benson **Second by:** J. Koller

AEGL 3 **Motion by:** _____ **Second by:** _____

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** 12/10/03 _____ **Date:** _____

NOTE: 22 Members, 17 VOTING

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: URANIUM HEXAFLUORIDE **CAS Reg. No.:**

Chemical Manager: George Rusch **Staff Scientist:** Cheryl Bast

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff			Y		Nancy Kim			Y	
Steven Barbee			Y		Loren Koller			Y	
Lynn Beasley			Y		Glenn Leach			A	
Robert Benson			Y		~~Mark McClanahan~~			~~A~~	
Jonathan Borak			Y		John Morawetz			Y	
William Bress			Y		Richard Niemeier			Y	
George Cushmac			Y		Marinelle Payton				
Ernest Falke			Y		Zarena Post				
Larry Gephart			A		George Rodgers			Y	
John Hinz			A		George Rusch, Chair			Y	
Jim Holler			Y		Robert Snyder				
Thomas Hornshaw			Y		Thomas Sobotka				
					Richard Thomas			Y	
					TALLY			17/17	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	~~,~~( )	~~,~~( )	,( )	,( )	,( )
AEGL 3	15,(220)	5.0,(72)	2.5,(36)	0.63,(9.0)	0.32(4.5)
LOA					

Revise n from 0.66 to n = 1.0

AEGL 1 **Motion by:** _____ **Second by:** _____

AEGL 2 **Motion by:** _____ **Second by:** _____

AEGL 3 **Motion by:** G. Alexeeff **Second by:** G. Rodgers

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 12/10/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: HYDROGEN IODIDE **CAS Reg. No.:**

Chemical Manager: Ernest Falke **Staff Scientist:** Sylvia Talmage

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	N				Nancy Kim	Y			
Steven Barbee	Y				Loren Koller	Y			
Lynn Beasley	Y				Glenn Leach	A			
Robert Benson	Y				Mark McClanahan	A			
Jonathan Borak	A				John Morawetz	N			
William Bress	Y				Richard Niemeier	Y			
George Cushmac	Y				Marinelle Payton	A			
Ernest Falke	N				~~Zarena Post~~				
Larry Gephart	A				George Rodgers	N			
John Hinz	Y				George Rusch, Chair	Y			
Jim Holler	Y				Robert Snyder				
Thomas Hornshaw	Y				Thomas Sobotka				
					Richard Thomas	N			
					TALLY	12/17			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	1 ,( )	1 ,( )	1 ,( )	) ,( )	) ,( )
AEGL 2	100,( )	43 ,( )	22 ,( )	11 ,( )	11 ,( )
AEGL 3	744( )	250,( )	120 ,( )	31 ,( )	31 ,( )
LOA					

* Values based on HBr (no info. to develop a table for HI)

AEGL 1 Motion by: R. Niemeier **Second by:** John Hinz

AEGL 2 Motion by: _____ **Second by:** _____

AEGL 3 Motion by: _____ **Second by:** _____

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/10/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: DISULFUR DICHLORIDE **CAS Reg. No.:**

Chemical Manager: **Staff Scientist:** KOWETHA DAVIDSON

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff					Nancy Kim				
Steven Barbee					Loren Koller				
Lynn Beasley					Glenn Leach				
Robert Benson					Mark McClanahan				
Jonathan Borak					John Morawetz				
William Bress					Richard Niemeier				
George Cushmac					Marinelle Payton				
Ernest Falke					Zarena Post				
Larry Gephart					George Rodgers				
John Hinz					George Rusch, Chair				
Jim Holler					Robert Snyder				
Thomas Hornshaw					Thomas Sobotka				
					Richard Thomas				
					TALLY				

Check with author of sole lit. paper

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					

AEGL 1 Motion by: _____ **Second by:** _____

AEGL 2 Motion by: _____ **Second by:** _____

AEGL 3 Motion by: _____ **Second by:** _____

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** _____

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: SULFUR DICHLORIDE **CAS Reg. No.:**

Chemical Manager: K **Staff Scientist:** KOWETHA DAVIDSON

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff					Nancy Kim				
Steven Barbee					Loren Koller				
Lynn Beasley					Glenn Leach				
Robert Benson					Mark McClanahan				
Jonathan Borak					John Morawetz				
William Bress					Richard Niemeier				
George Cushmac					Marinelle Payton				
Ernest Falke					Zarena Post				
Larry Gephart					George Rodgers				
John Hinz					George Rusch, Chair				
Jim Holler					Robert Snyder				
Thomas Hornshaw					Thomas Sobotka				
					Richard Thomas				
					TALLY				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					

No producer or toxicity data - PUT ON HOLDING STATUS

AEGL 1 **Motion by:** _____ **Second by:** _____

AEGL 2 **Motion by:** _____ **Second by:** _____

AEGL 3 **Motion by:** _____ **Second by:** _____

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/10/03

NAC/AEGL Meeting 31: December 10-12, 2003

Appendix I

Chemical: CHLOROACETYL CHLORIDE **CAS Reg. No.:**

Chemical Manager: STEVE BARBEE **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1 (0.04 *)	AEGL2	AEGL3	LOA
George Alexeeff	N	P	N	
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	P	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	P	P	P	
William Bress	N	N	Y	
George Cushmac	N	Y	Y	
Ernest Falke	Y	N	Y	
Larry Gephart				
John Hinz	Y	Y	Y	
Jim Holler	Y	Y	Y	
Thomas Hornshaw	N	N	Y	

NAC Member	AEGL1 *	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Loren Koller	N	Y	Y	
Glenn Leach	A			
Mark McClanahan				
John Morawetz	N	P	N	
Richard Niemeier	N	N	P	
Marinelle Payton				
Zarena Post				
George Rodgers	Y	N	Y	
George Rusch, Chair	Y	Y	Y	
Robert Snyder	P			
Thomas Sobotka				
Richard Thomas	Y	Y	P	
TALLY	11/17 11/15	10/15	13/15	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~0.08~~ (*0.04)	~~0.08~~ (*0.04)	~~0.08~~ (*0.04)	~~0.06~~ (*0.04)	~~0.08~~ (*0.04)
AEGL 2	2.9, ( )	2.0, ( )	~~1.60~~, (1.60)	0.40, ( )	0.20, ( )
AEGL 3	95, ( )	66, ( )	50, ( )	13, ( )	6.5, ( )
LOA					

* passed (2nd vote on AEGL-1)

AEGL 1 Motion by: J. Hinz **Second by:** Benson

AEGL 2 Motion by: Benson **Second by:** Hinz

AEGL 3 Motion by: Benson **Second by:** Hinz

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/10/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: DICHLOROACETYL CHLORIDE **CAS Reg. No.:**

Chemical Manager: STEVE BARBEE **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1 *	AEGL2	AEGL3	LOA
George Alexeeff	P	P	Y	
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	P	P	P	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Larry Gephart			A	
John Hinz	A	A	A	
Jim Holler	Y	Y	Y	
Thomas Hornshaw	Y	Y	Y	

Unavailable

NAC Member	AEGL1 *	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Loren Koller	Y	Y	Y	
Glenn Leach		A	A	
Mark McClanahan			A	
John Morawetz	Y	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton				
Zarena Post				
George Rodgers	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Robert Snyder				
Thomas Sobotka				
Richard Thomas	Y	Y	Y	
TALLY	14/14	14/14	15/15	

Unavailable

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
*AEGL 1	NR, (0.040) **	NR, (0.040) **	NR, (0.040) **	NR, (0.040) **	NR, (0.040) **
*AEGL 2	2.9, ( )	2.0, ( )	1.6, ( )	0.40, ( )	0.20, ( )
*AEGL 3	95, ( )	66, ( )	52, ( )	13, ( )	6.5, ( )
LOA					

* UNANIMOUS NR FOR LACK OF DATA
** $CICH_2COCl$ is somewhat more toxic, but adopt these values by analogy

AEGL 1 Motion by: Benson ** Falke **Second by:** Koller ** Koller

AEGL 2 Motion by: Barbee **Second by:** Bress

AEGL 3 Motion by: Alexeeff **Second by:** Thomas

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/11/03
12/11/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: TRICHLOROACETYL CHLORIDE **CAS Reg. No.:**

Chemical Manager: STEVE BARBEE **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y				Nancy Kim	Y			
Steven Barbee	Y				Loren Koller	Y			
Lynn Beasley	Y				Glenn Leach				
Robert Benson	Y				Mark McClanahan				
Jonathan Borak	A				John Morawetz	Y			
William Bress	Y				Richard Niemeier	Y			
George Cushmac	Y				Marinelle Payton				
Ernest Falke	Y				Zarena Post				
Larry Gephart					George Rodgers	Y			
John Hinz	A				George Rusch, Chair	Y			
Jim Holler	Y				Robert Snyder				
Thomas Hornshaw	Y				Thomas Sobotka				
					Richard Thomas	Y			
					TALLY	16/16			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					

* NR due to lack of data (TABLE CHEMICAL) - INCLUDE IN CHLOROACETYL CHLORIDE DOCUMENT

AEGL 1 **Motion by:** _____ **Second by:** _____

AEGL 2 **Motion by:** _____ **Second by:** _____

AEGL 3 **Motion by:** _____ **Second by:** _____

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/11/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: ACETYL CHLORIDE **CAS Reg. No.:**

Chemical Manager: STEVE BARBEE **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff					Nancy Kim				
Steven Barbee					Loren Koller				
Lynn Beasley					Glenn Leach				
Robert Benson					Mark McClanahan				
Jonathan Borak					John Morawetz				
William Bress					Richard Niemeier				
George Cushmac					Marinelle Payton				
Ernest Falke					Zarena Post				
Larry Gephart					George Rodgers				
John Hinz					George Rusch, Chair				
Jim Holler					Robert Snyder				
Thomas Hornshaw					Thomas Sobotka				
					Richard Thomas				
					TALLY				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					

NR - LACK OF DATA - INCLUDE IN CHLOROACETYL CHLORIDE DOCUMENT

AEGL 1 Motion by: Falke **Second by:** Thomas

AEGL 2 Motion by: _____ **Second by:** _____

AEGL 3 Motion by: _____ **Second by:** _____

LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/11/03

Appendix M

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: METHACRYLONITRILE **CAS Reg. No.:** 126-98-7

Chemical Manager: George Rodgers **Staff Scientist:** Cheryl Bust

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A	A	A	
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	P	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Faike	Y	Y	Y	
Larry Gephart	A	A	A	
John Hinz	Y	Y	P	
Jim Holler	Y	Y	Y	
Thomas Hornshaw	Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	P	
Loren Koller	Y	Y	Y	
Glenn Leach	A	A	A	
Mark McClanahan	A	A	A	
John Morawetz	Y	Y	N	
Richard Niemeier	Y	[illegible]	A	
Marinelle Payton	A	A	A	
Zarena Post	A	A	A	
George Rodgers	Y	Y	Y	
George Rusch, Chair	Y	P	P	
Robert Snyder	A	A	A	
Thomas Sobotka	A	A	A	
Richard Thomas	Y	Y	Y	
TALLY	15/15	15/15	11/12	

PPM, (mg/m³)	10 Min	30 Min	1Hr	4 Hr	8 Hr
AEGL 1	2.0, ( )	2.0, ( )	[illegible], (1.0)	1.0, ( )	1.0, ( )
AEGL 2	16, ( )	16, ( )	13, ( )	6.5, ( )	6.5, ( )
AEGL 3	32, ( )	32, ( )	25, ( )	13, ( )	13, ( )
LOA					

AEGL 1 Motion by: Rodgers **Second by:** Koller

AEGL 2 Motion by: Benson **Second by:** Rodgers

AEGL 3 Motion by: Faike **Second by:** Rodgers

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/12/03

NAC/AEGL Meeting 31: December 10-12, 2003

Chemical: BENZONITRILE **CAS Reg. No.:**

Chemical Manager: Rodgers **Staff Scientist:** Barr

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A	A	A		Nancy Kim	Y	N	Y	
Steven Barbee	Y	Y	Y		Loren Koller	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Mark McGlanahan	A	A	-	
Jonathan Borak	A	A	A		John Morawetz	Y	Y	Y	
William Bress	Y	N	N		Richard Niemeier	Y	Y	Y	
George Cushmac	Y	Y	Y		Marinelle Payton	A	A	A	
Ernest Falke	Y	Y	Y		Zarena Post	A	A	-	
Larry Gephart	A	A	A		George Rodgers	Y	Y	Y	
John Hinz	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Jim Holler	Y	Y	Y		Robert Snyder	A	A	A	
Thomas Hornshaw	Y	Y	Y		Thomas Sobotka	A	A	-	
					Richard Thomas	Y	Y	Y	
					TALLY	16/16	14/16	13/16	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	39, ( )	27, ( )	22, ( )	11, ( )	5.6, ( )
AEGL 3	100, ( )	71, ( )	56, ( )	23, ( )	11, ( )
LOA					

AEGL 1 **Motion by:** Benson **Second by:** Falke

AEGL 2 **Motion by:** Rodgers **Second by:** Benson

AEGL 3 **Motion by:** Benson **Second by:** Rodgers

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 12/12/03