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

December 5-7, 2007

Meeting-44 Highlights

Orlando World Center Marriott
8701 World Center Drive
Orlando, FL

INTRODUCTION

Ernest Falke distributed a CD containing the most recent Technical Support Documents for all AEGL program chemicals that are proposed, interim, or final status. Dr. Falke also stated that the Prepublication Copy of NAS Volume 6 was released in September, 2007, and that the published volume should be available for distribution by the March meeting.

Paul Tobin informed the group that the NAC/AEGL committee was recognized by the FACA awards program twice (last year and this year). There are 27 EPA FACAs, and only the NAC/AEGL was recognized twice; a total of only 3 EPA FACAs were recognized. Specifically, the NAC/AEGL was recognized for timeliness of Federal Register notices, transparency of the process, public input (both via the meeting and the Federal Register), and international impact.

The draft NAC/AEGL-43 meeting highlights were reviewed. Due to a rounding error, the 30-minute AEGL-3 value for dichlorosilanes should be 110 ppm, not 105 ppm. A motion was made by Bob Benson and seconded by John Hinz to accept the minutes as proposed with the aforementioned correction. The motion passed unanimously by a show of hands (Appendix A). The Final NAC/AEGL-43 meeting highlights are attached (Appendix B).

The highlights of the NAC/AEGL-44 meeting are summarized below along with the Meeting Agenda (Attachment 1) and the Attendee List (Attachment 2). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-44 Agenda.

Paul Tobin addressed the committee regarding George Woodall's question on how to clarify the AEGL-1 definition to EPA. The approach recommended was that George Woodall prepare a letter directed to the AEGL committee requesting guidance, making sure that it is within the scope of the charter. George Rusch will lead the discussion and seek consensus. Finally, the recommendation of the AEGL committee will be communicated to the EPA administrator. Paul Tobin needs to ask whether the NAS can be copied on the letter.

NO DATA CHEMICALS

Chloropivaloyl chloride (CAS No. 4300-97-4)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA; George Rusch, Honeywell Corp.

There are no data currently available for development of AEGL values for chloropivaloyl chloride. A motion was made by John Hinz and seconded by Bob Benson to table deliberations and place this chemical in holding status. The motion passed unanimously by a show of hands (Appendix C).

Ethylene fluorohydrin (CAS No. 371-62-0)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA; George Rusch, Honeywell Corp.

There are no data currently available for development of AEGL values for ethylene fluorohydrin. A motion was made by John Hinz and seconded by Bob Benson to table deliberations and place this chemical in holding status. The motion passed unanimously by a show of hands (Appendix D).

Thiophosgene (CAS No. 463-71-8)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA; George Rusch, Honeywell Corp.

There are no data currently available for development of AEGL values for thiophosgene. A motion was made by John Hinz and seconded by Bob Benson to table deliberations and place this chemical in holding status. The motion passed unanimously by a show of hands (Appendix E).

REVIEW of FEDERAL REGISTER-10 COMMENTS

Thirty-seven chemicals were included in the FR10 publication. The 36 chemicals not receiving comments are elevated to interim status. Chemicals elevated to interim status include: 1,2,3-Trimethylbenzene (526-73-8); 1,2,4-Trimethylbenzene (95-63-6); 1,3,5-Trimethylbenzene (108-67-8); Adamsite (578-94-9); Aluminum phosphide (20859-73-8); Arsenic trioxide (1327-53-3); Biphenyl (92-52-4); bis-Chloromethyl ether (542-88-1); Calcium phosphide (1305-99-3); Cyclohexyl isocyanate (3173-53-3); Diphenylchloroarsine (712-48-1); Ethyldichloroarsine (598-14-1); Hexafluoroacetone (684-16-2); Hexafluoropropylene (116-15-4); Ketene (463-51-4); Magnesium

aluminum phosphide (no CAS number); Magnesium phosphide (12057-74-8); Methyl chlorosilane (993-00-0); Methyl dichlorosilane (75-54-7); Methyldichloroarsine (593-89-5); Nitrogen mustard HN-1 (538-07-8); Nitrogen mustard HN-2 (51-75-2); Nitrogen mustard HN-3 (555-77-1); Phenyldichloroarsine (696-28-6); Phenyl mercaptan (108-98-5); Potassium phosphide (20770-41-6); Propargyl alcohol (107-19-7); Selenium hexafluoride (7783-79-1); Silane (7803-62-5); Sodium phosphide (12058-85-4); Strontium phosphide (12504-13-1); Sulfuryl chloride (7791-25-5); Tetramethoxy silane (681-84-5); Trimethoxy silane (2487-90-3); Vinyl acetate monomer (108-05-4); Zinc phosphide (1314-84-7).

Methyl t-butyl ether (MTBE) (CAS No. 1634-04-4)

Staff Scientist: Dana Glass, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Chemical Manager Bob Benson provided a summary of the single public comment (from Lyondell Chemical Company) received on MTBE (Attachment 3). The comment agreed with the AEGL values presented in the Technical Support Document. The comment also asked that the document be updated with additional information on human exposure and epidemiological studies, and requested clarification of some aspects of the genotoxicity data, carcinogenicity data, and the metabolism section. Lastly the comment asked for clarification of Appendix D on pharmacokinetic modeling. Dana Glass will update the document. As none of the requested changes will change the AEGL values, Bob Benson moved that MTBE be elevated to Interim Status, and Richard Niemeier seconded the motion. The motion passed unanimously (Appendix F).

REVIEW of COT COMMENTS

N,N-Dimethylformamide (CAS No. 68-12-2)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: George Woodall, U.S. EPA

Chemical manager George Woodall discussed COT comments for n,n-dimethylformamide (Attachment 4). The TSD was returned for consideration of developmental endpoints and concern over the derivation of AEGL-2 values. After George presented the comments and possible alternative AEGL derivations, a motion was made by Bob Benson and seconded by John Hinz to reassess the AEGL values. The motion passed unanimously by a show of hands (Appendix G). It was proposed that the AEGL-1 values would remain as Not Recommended due to insufficient data. Revised AEGL-2 values were based on a point-of-departure of 150 ppm for 6-hours (NOEL for developmental malformations in rabbits) (Hellwig et al., 1991). A total uncertainty factor of 3 was applied (Interspecies of 1 because it is expected that humans are less sensitive than rabbits. Intraspecies of 3 because use of the default of 10 produces AEGL values that are inconsistent with

the overall database). Values were scaled across time using the default values of n = 1 or n = 3. The 30-min value was adopted as the 10-min value. Revised AEGL-3 values were based on a 3-hour no effect level for mortality in rats of 3700 ppm (MacDonald, 1982). A total uncertainty factor of 10 was applied (interspecies of 1 because it is expected that humans are less sensitive than rabbits, and the default intraspecies of 10). Values were scaled across time using the default values of n = 1 or n = 3. After discussion, a motion was made by Ernie Falke and seconded by Dieter Heinz to adopt the alternative AEGL-1, AEGL-2, and AEGL-3 values as presented. The motion passed unanimously (YES: 23; NO: 0; ABSTAIN: 0; Appendix G). Marcel van Raaij pointed out that the developmental effects seen in the study used for AEGL-2 were substantial effects, and that these effects may not be apparent after a single exposure to dimethylformamide. A statement to this effect should be included in the revised TSD. Calvin Willhite requested two additions to the document: (1) carcinogenicity: there is the pre-requisite to have hepatic damage for cancer. If one is protected against hepatic damage, then cancer is avoided; (2) the Research Needs section should have a statement indicating that a PBPK model is needed for this chemical.

Summary of AEGL Values for n,n-Dimethylformamide						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	-
AEGL-2 (Disabling)	110 ppm	110 ppm	91 ppm	57 ppm	38 ppm	Protection against developmental effects in rabbits (Hellwig et al., 1991)
AEGL-3 (Lethal)	970 ppm	670 ppm	530 ppm	280 ppm	140 ppm	3-hr NOEL for lethality in rats (MacDonald, 1982)

CHEMICAL REVISITS/STATUS UPDATES

Agent VX (CAS No. 50782-69-9)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Glenn Leach, U.S. Army

Bob Young summarized the recent studies on the nerve agent VX that have become available (Attachment 5). These data were evaluated and analyzed with respect to the previously published (NRC, 2003) AEGL values for VX. AEGL-1 values developed using recent data of Benton et al. (2006a) would eliminate the MF and use a VX-specific "*n*" of 1.65 (for miosis) resulting in slightly greater (8-hr value is slightly lower) but operationally equivalent values. Published AEGL-1 values (NRC, 2003) are protective and validated by the new data. For AEGL-2, the new data (Benton et al., 2006a; Genovese et al., 2007) would result in slightly increased AEGL-2 values (operationally equivalent) due to interspecies UF of 3 vs 1 and time-scaling "*n*" value of 1.65 vs 2. Both the published (NRC, 2003) and new values address peripheral neuromuscular effects as well as miosis. Published values are more protective and validated by new data. For AEGL-3, new data from Benton et al. (2006b) would justify elimination of the MF for a sparse database. Time scaling "*n*" of 0.92 vs 2 results in slightly lower values for the 4-hr and 8-hr durations but slightly higher values for the durations of 1 hour and less. However, the "*n*" of 0.92 may be a function of percutaneous absorption. The published values are sufficiently protective. Overall, the new data support the approach/rationale used to develop the AEGL values for VX as published by the National Research Council. A motion was made by Bob Benson and seconded by John Hinz to reaffirm the published AEGL values for Agent VX and not to revise the AEGL values. The motion passed (YES: 20; NO: 1; ABSTAIN: 0; Appendix H). Ernie Falke and Bob Young will work together to find a transparent way to communicate this information to interested parties. Suggestions included an addendum to the NRC publication, a journal publication, FR publication, or some combination of the above.

Tetrachloroethylene (CAS No. 127-18-4)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: Bob Benson, U.S. EPA

This chemical was deferred until NAC-45 (March, 2008) for PBPK modeling.

1,1,1-Trichloroethane (CAS No. 71-55-6)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bob Benson, U.S. EPA

This chemical was deferred until NAC-45 (March, 2008) for PBPK modeling.

REVIEW of PRIORITY CHEMICALS

4 Selected Chlorosilanes

Diethyl dichlorosilane (CAS NO. 1719-53-5)
Dimethylchlorosilane (CAS NO. 1066-35-9)
Ethyl trichlorosilane (CAS NO. 115-21-9)
Methylvinyl dichlorosilane (CAS NO. 124-70-9)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA

Cheryl Bast summarized the data in the TSD (Attachment 6), and explained that at NAC-43, AEGL values were derived for 17 chlorosilanes. The four chlorosilanes being deliberated at NAC-44 will be added to the "Selected Chlorosilanes" TSD. The chlorosilanes are corrosive, and inhalation exposure may cause nasal, throat, or lung irritation, coughing, wheezing, and /or shortness of breath. Chlorosilanes react rapidly with water, steam, or moisture and decompose to form hydrogen chloride gas and silanols, which condense spontaneously to form highly cross-linked polymeric gels. Although chemical-specific data are not available for many of the title chlorosilanes, acute inhalation data from rat studies are available for structurally-similar chlorosilanes (n-propyltrichlorosilane, methyltrichlorosilane, vinyltrichlorosilane, ethyltrichlorosilane, methylvinyldichlorosilane, methyldichlorosilane, dimethyldichlorosilane, dimethylchlorosilane, and trimethylchlorosilane). These data suggest that the acute toxicity of monochlorosilanes, dichlorosilanes, and trichlorosilanes is due to the hydrogen chloride hydrolysis product; acute toxicity of these chlorosilanes is both qualitatively (based on clinical signs) and quantitatively (based on molar equivalents of hydrogen chloride) similar to that of HCl (Jean et al., 2006). Complete hydrolysis of one mole of a monochlorosilane would yield a maximum of one mole of hydrogen chloride. Complete hydrolysis of a dichlorosilane would yield a maximum of two moles of hydrogen chloride, and complete hydrolysis of a trichlorosilane would yield a maximum of three moles of hydrogen chloride. Therefore, hydrogen chloride AEGL values are proposed as AEGL values for monochlorosilanes. Proposed AEGL values for dichlorosilanes were derived by dividing the hydrogen chloride AEGL values by a molar adjustment factor of two, and similarly, proposed AEGL values for the title trichlorosilanes were derived by dividing the hydrogen chloride AEGL values by a molar adjustment factor of three. A motion was made by Bob Benson and seconded by Dieter Heinz to adopt AEGL-1, AEGL-2, and AEGL-3 values for all 4 chlorosilanes as proposed. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix I for diethyldichlorosilane; Appendix J for dimethyldichlorosilane; Appendix K for ethyltrichlorosilane; Appendix L for methylvinyldichlorosilane).

Summary of AEGL Values Selected Chlorosilanes							
Compound	**Classification**	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
MONOCHLOROSILANES Dimethylchlorosilane	AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	Hydrogen chloride (HCl) AEGL-1 values adopted as AEGL-1 values for Monochlorosilanes (NRC, 2004)
	AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Hydrogen chloride (HCl) AEGL-2 values adopted as AEGL-2 values for Monochlorosilanes (NRC, 2004)
	AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	Hydrogen chloride (HCl) AEGL-3 values adopted as AEGL-3 values for Monochlorosilanes (NRC, 2004)
DICHLOROSILANES Diethyl dichlorosilane Methylvinyl dichlorosilane	AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 2 adopted as AEGL-1 values for Dichlorosilane (NRC, 2004)
	AEGL-2	50 ppm	22 ppm	11 ppm	5.5 pm	5.5 ppm	Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 2 adopted as AEGL-2 values for Dichlorosilane (NRC, 2004)
	AEGL-3	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm	Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 2 adopted as AEGL-3 values for Dichlorosilane (NRC, 2004)
TRICHLOROSILANES Ethyltrichlorosilane	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	Hydrogen chloride AEGL-1 values divided by a molar adjustment factor of 3 adopted as AEGL-1 values for Trichlorosilanes (NRC, 2004)
	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 pm	3.7 ppm	Hydrogen chloride AEGL-2 values divided by a molar adjustment factor of 3 adopted as AEGL-2 values for Trichlorosilanes (NRC, 2004)
	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm	Hydrogen chloride AEGL-3 values divided by a molar adjustment factor of 3 adopted as AEGL-3 values for Trichlorosilanes (NRC, 2004)

Carbonyl Fluoride (CAS No. 353-50-4)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

Jennifer Rayner summarized the data in the TSD (Attachment 7). Data are sparse for this chemical, and AEGL-1 values were not proposed due to insufficient data. Proposed AEGL-2 values (1.0, 0.70, 0.56, 0.33, and 0.17 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were derived by dividing the proposed AEGL-3 values by 3. Proposed AEGL-3 values (3.0, 2.1, 1.7, 1.0, and 0.52 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a 4-hour BMC_{01} of 10.4 ppm (DuPont, 1976). An intraspecies UF of 3 was proposed and was considered sufficient due to the steep concentration-response curve. An interspecies UF of 3 was also proposed because portal of entry effects from contact irritation are not expected to vary greatly between species. Scaling of values across time utilized the default values of n =3 or n =1. After discussion, a motion was made by Bob Benson and seconded by Richard Niemeier to adopt AEGL-3 values of (1.0, 1.0, 0.83, 0.52, and 0.26 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) based on the calculated $BMCL_{05}$ of 5.2 ppm from the 4-hr DuPont (1976) rat study as the point of departure for AEGL-3. Uncertainty factor application and time scaling are as proposed, except that the 30-min AEGL-3 value is adopted as the 10-min value because the point of departure is 4-hours. The motion passed (YES: 21; NO: 0; ABSTAIN: 0; Appendix M). A motion was then made by Bob Benson and seconded by Dieter Heinz to derive AEGL-2 values by dividing the AEGL-3 values by 3. The steep concentration-response curve should be included in the rationale. The motion passed (YES: 21; NO: 0; ABSTAIN: 0; Appendix M). Finally, a motion was made by Bob Benson and seconded by Gail Chapman to not recommend AEGL-1 values due to insufficient data. The motion passed (YES: 21; NO: 0; ABSTAIN: 0; Appendix M). In order to strengthen the TSD, DuPont will be contacted about occupational measurements. If no data are obtained, it will be acknowledged that there is no further information about occupational values.

Summary of AEGL Values for Carbonyl Fluoride						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	0.35 ppm	0.35 ppm	0.28 ppm	0.17 ppm	0.087 ppm	One-third the AEGL-3 values (NRC, 2001)
AEGL-3	1.0 ppm	1.0 ppm	0.83 ppm	0.52 ppm	0.26 ppm	4-hr rat $BMCL_{05}$ (DuPont, 1976)

Stibine (CAS No. 7803-52-3)

Staff Scientist: Jennifer Rayner, ORNL

AEGL-44 FINAL

Chemical Manager: Marcel van Raaij, RIVM

Jennifer Rayner presented a summary of the available data and an overview of the development of proposed AEGL values for stibine (Attachment 8). AEGL-1 values were not recommended because of insufficient data. Proposed AEGL-2 values (4.2, 2.9, 1.5, 0.36, and 0.18 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on the highest experimental concentration (29.1 ppm for 30 min) without AEGL-2 effects (eye closure, generalized depressed activity) in rats and guinea pigs. A total uncertainty factor of 10 was proposed to account for interspecies extrapolation and intraspecies variability. A factor of 3 was proposed for interspecies variability. In addition to dog and cat differences, Webster (1946) noted that three- or four-fold higher concentrations were needed to produce death in guinea pigs, however, the studies were not well documented. An uncertainty factor of 3 was proposed to account for intraspecies variability to protect sensitive individuals and reflect individual variability. Although the mechanism of toxicity is unknown, it is unlikely that the response of normal and sensitive or susceptible individuals would differ significantly because the respiratory irritant action is not expected to vary much among individuals. Scaling of values across time utilized the default values of n =3 or n =1. Proposed AEGL-3 values (23, 16, 8.1, 2.0, and 1.0 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a 30-min $BMCL_{05}$ of 161 ppm in rats. Uncertainty factor application and time scaling was proposed as for AEGL-2. After discussion, a motion was made by Bob Benson and seconded by Henry Anderson to base AEGL-3 values (28, 19, 9.6, 2.4, and 1.2 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) on a point of departure of 191 ppm, the no effect level for lethality seen in rats and guinea pigs at 30 min, because raw data were insufficient for BMC analysis. Time scaling and UF application remained as proposed. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix N). A motion was then made by Bob Benson and seconded by David Freshwater to adopt AEGL-2 values as proposed The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix N). Finally, a motion was made by Bob Benson and seconded by Dieter Heinz to adopt not recommended for AEGL-1. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix N). When the TSD is revised, the intraspecies UF of 3 should be supported by indicating that the POD is based on pulmonary irritation, an endpoint that typically has used an intraspecies UF of 3. In addition, the factor of 3 is also supported by the steep-concentration response apparent in two species (rats and guinea pigs) as shown by Price et al. (1979). In this study, rats and guinea pigs exposed to 191 ppm for 30 min showed no lethality. A ~2 fold increase in concentration (333 ppm) showed 70 and 80% lethality due to pulmonary edema in rats and guinea pigs, respectively, supporting a sharp concentration-response at 30 minutes.

Summary of AEGL Values for Stibine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL–2	4.2 ppm	2.9 ppm	1.5 ppm	0.36 ppm	0.18 ppm	NOEL for eye closure and depressed activity in rats (Price et al., 1979)
AEGL–3	28 ppm	19 ppm	9.6 ppm	2.4 ppm	1.2 ppm	Concentration showing no lethality in rats and guinea pigs (191 ppm for 30 min) (Price et al., 1979)

Boron Tribromide (CAS No. 10294-34-5)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Chemical manager Bob Benson gave a brief history of previous committee consideration of this chemical. There are no published toxicity data on this chemical. At NAC-43, the committee deferred action because of questions about the extent of hydrolysis to hydrogen bromide. The manufacturer, Albemarle Corporation, submitted a letter stating that in the presence of water conversion of Boron Tribromide to hydrogen bromide is complete. Sylvia Talmage provided a summary of the Technical Support Document (Attachment 9). All of the AEGL values are based on analogy with hydrogen bromide. After discussion, Marcel vanRaaij moved that all AEGL values be based on 1/3 of the hydrogen bromide values and that the values for Boron Tribromide would be adjusted if the hydrogen bromide values changed. Susan Ripple seconded the motion. The motion passed (YES, 21; NO, 0; ABSTAIN: 1; Appendix O).

Summary of AEGL Values for Boron tribromide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	1/3 the HBr AEGL-1 values
AEGL–2	33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm	1/3 the HBr AEGL-2 values
AEGL–3	250 ppm	83 ppm	40 ppm	10 ppm	10 ppm	1/3 the HBr AEGL-3 values

Chloropicrin (CAS No. 6581-06-2)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Gail Chapman, U.S. Navy

Susan Ripple made a brief presentation about a new methodology to evaluate sensory irritation (Cain method). Calvin Willhite requested that details of this new methodology be included in the chloropicrin document. The committee agreed with Calvin, and Susan will send a publication to Bob that contains the details of the methodology, so this information may be included in the technical support document.

An overview of the available data and the derivation of draft AEGL values were then provided by Bob Young (Attachment 10). Proposed AEGL-1 values (0.15, 0.097, 0.073, 0.041, and 0.031 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a $BMCL_{10}$ of 0.073 ppm for ocular irritation in human volunteers exposed to chloropicrin for up to 30 minutes (Reeves, 2006a). An interspecies UF of 1 was proposed because the subjects were human volunteers and included sensitive individuals. Time scaling AEGL-specific durations used the equation $C^n \times t = k$, where n= 2.4 was empirically determined from the concentration-time relationship of rat lethality data. Proposed AEGL-2 values (0.32, 0.20, 0.15, 0.084, and 0.063 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on intolerable ocular irritation and a threshold for ventillary effects in human volunteers (0.15 ppm for 60 min; Reaves et al., 2006b). Uncertainty factor application and time scaling were as described as for AEGL-1. Proposed AEGL-3 values (3.0, 1.9, 1.4, 0.79, and 0.59 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a 4-hour rat $BMCL_{05}$ of 7.5 ppm (Yoshida et al., 1987a; 1991). An interspecies UF of 3 was applied because the variability in lethal response was not great and the 3-fold adjustment was sufficient for dosimetric variability across species. An intraspecies UF of 3 was also applied because lethality is due to respiratory damage from contact with epithelial surfaces. Time scaling is as described above.

After extensive discussion, concern about the BMC calculation for ocular irritation, Bob Benson moved (seconded by Calvin Willhite) that AEGL-1 values of 0.050 ppm be adopted for all time points. The point of departure is a NOEL of 0.050 ppm for irritation in human volunteers (Reaves, 2006); the threshold for irritation was 0.075 ppm. Inter- and intraspecies uncertainty factors were 1 each as described above. The motion passed (YES: 19; NO: 0; ABSTAIN: 1; Appendix P). A motion was then made by Bob Benson and seconded by Richard Niemeier to adopt AEGL-2 values of 0.15 ppm at all time points. The point of departure is a threshold for intolerable irritation/sporadic severe eye irritation in human volunteers at 0.15 ppm (Reaves, 2006). Inter- and intraspecies uncertainty factors were 1 each as described above. The motion passed (YES: 20; NO: 2; ABSTAIN: 1; Appendix P). Finally, a motion was made by Bob Benson and seconded by Marcel van Raaij to adopt AEGL-3 values (2.0, 2.0, 1.4, 0.79, and 0.58 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) based on a calculated 4-hr rat $BMCL_{05}$ of 7.9 ppm. Time scaling was accomplished using a value of n = 2.3. The value of n changed to n=2.3 and the POD was developed from the BMC analysis of the 4-hr data from Yoshida 1987a and Yoshida 1991. Only whole body data were used for these calculations and data were from vapor studies, not aerosol

studies. The calculation of n was derived from 240 min and 30 min data using the ten Berge software. The analysis started by assessing all of the raw data available but the probability of the model was poor. Further analysis was performed with different combination of data and finally an n=2.3 was obtained with a probability of the model increasing. The motion passed (YES: 22; NO: 0; ABSTAIN: 1; Appendix P).

Summary of AEGL Values for Chloropicrin						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm	0.05 ppm	NOEL for eye irritation in human volunteers (Reaves, 2006)
AEGL–2	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	Sporadic/severe eye irritation in human volunteers (Reaves, 2006)
AEGL–3	2.0 ppm	2.0 ppm	1.4 ppm	0.79 ppm	0.58 ppm	4-hr rat $BMCL_{05}$ (Yoshida et al., 1987a; 1991)

Methyl iodide (CAS No. 74-88-4)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Alan Becker, Florida

Mike Aerts of the Florida Fruit & Vegetable Association gave a presentation on how methyl iodide is applied to fields in Florida. Color-coded “pig” containers containing 1100-1500 lbs methyl iodide are shipped in rail cars to distribution centers. Fumigants or odorants such as chloropicrin (2-67%) are added at the distribution centers. Methyl iodide is machine-applied as a liquid incorporated into the soil (shank application) and immediately covered by soil. Soil moisture is kept at field capacity with a field trickle irritation system. Offgassing starts at 24 hours, and planting takes place one to two weeks later. There is a 5-day period before fields are re-entered. Applicators do not wear protective clothing or masks. Monitoring data have been supplied to U.S. EPA.

Sylvia Talmage reviewed the data set for methyl iodide (Attachment 11). Proposed values were based on olfactory irritation. Marcel van Raaij pointed out the susceptibility of the developing fetus to methyl iodide. This effect may be attributed to the iodine released from methyl iodide on the developing thyroid, as studies with methyl chloride and methyl bromide did not show developmental toxicity. Calvin Willhite provided contact information for an oral iodine risk assessment document

developed by NSF International. This document may provide information on the levels of administered iodine associated with fetal thyroid toxicity. The chemical was tabled until the new information could be obtained and incorporated into the TSD.

Allyl chloride (CAS No. 107-05-1)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Richard Niemeier, NIOSH

Jennifer Rayner presented an overview of relevant data and development of the draft AEGL values (Attachment 12). Proposed AEGL-1 values were based on exposures experienced by human volunteers for 1-5 min (Torkelson et al. 1959; Shell Chemical Co. 1959). A few minutes of exposure to 3 ppm did not cause respiratory, eye, or nose irritation. However, the garlic-like odor of allyl chloride could be detected at this concentration. At higher concentrations, nose irritation and pulmonary discomfort occurred. An intraspecies uncertainty factor of 3 was proposed to protect sensitive individuals, but no factor was applied for species differences because human data were used. The AEGL-1 value of 1 ppm (3.1 mg/m^3) was held constant across all exposure time points because mild irritant effects generally do not vary greatly over time. Proposed AEGL-2 values (69, 69, 54, 34, and 22 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on exposure data showing no incapacitating or irreversible effects as there were no experimental data reporting AEGL-2 level effects. Female rats displayed very minimal acute renal tubular degeneration after a 6-hr exposure to 300 ppm allyl chloride whereas male rats were affected at 500 ppm (Quast et al. 1982a). Diarrhea, lethargy, and moderate eye closure were observed in both sexes at 500 ppm. A factor of 3 was proposed for the interspecies uncertainty and a factor of 3 for intraspecies uncertainty. In the Adams et al. study (1940), the guinea pig was the most sensitive species, but the sensitivity is less than twice the sensitivity of the rat which is being used to derive AEGL-3 values. The mechanism of action is not expected to differ between species. Data on asthmatics after exposure to allyl chloride are not available, so it is unknown if they are more susceptible to allyl chloride than healthy individuals. An intraspecies factor of 3 was proposed to protect sensitive individuals. Temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001). The 30-minute AEGL-2 value was adopted for the 10-minute value.

Proposed AEGL-3 values (180, 180, 140, 90, and 60 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on the highest experimental concentration (800 ppm) causing no lethality in rats exposed to allyl chloride for 6 hr (Quast et al. 1982a). A 4-hr exposure to 290 ppm produced 20% mortality (Adams et al. 1940), but the study quality was poor. Uncertainty factor application and time scaling as are described for AEGL-2. After discussion, a motion was made by John Hinz and seconded by Marcel van Raaij to adopt AEGL-1 values of 2.8 ppm across all time points. The rationale is as follows: Noticeable irritation of the sensory organs for most people occurred at concentrations ranging from 25-100 ppm. Minimal AEGL-1 effects were seen at 25 ppm. An estimated threshold was obtained by dividing 25 ppm by 3, yielding a threshold for

irritation of 8.3 ppm. Assuming that the noticeable irritation was for most people but no sensitive populations, an intraspecies UF of 3 was additionally added to the derivation to protect susceptible individuals. Calculations after UF applications yielded AEGL-1 values of 2.8 ppm for all time points. The motion passed (YES: 20; NO: 0; ABSTAIN: 2; Appendix Q). A motion was then made by Richard Niemeier and seconded by Lynn Beasley to adopt AEGL-2 values as proposed. The motion passed (YES: 20; NO: 0; ABSTAIN: 2; Appendix Q). Finally, a motion was made by John Hinz and seconded by Dieter Heinz to adopt AEGL-3 values as proposed. The motion passed (YES: 21; NO: 0; ABSTAIN: 0; Appendix Q).

Summary of AEGL Values for Allyl chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	2.8 ppm	2.8 ppm	2.8 ppm	2.8 ppm	2.8 ppm	Estimate of the threshold for irritation (Shell Chem. Co. 1959)
AEGL–2	69 ppm	69 ppm	54 ppm	34 ppm	22 ppm	Highest concentration with no irreversible or incapacitating effects (Quast et al. 1982a)
AEGL–3	180 ppm	180 ppm	140 ppm	90 ppm	60 ppm	Highest concentration with no lethality (Quast et al. 1982a)

Methanesulfonyl chloride (CAS No. 124-63-0)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Roberta Grant, TDEQ

Cheryl Bast reviewed the limited data set for methanesulfonyl chloride (Attachment 13). Data were insufficient to derive AEGL-1 values for methanesulfonyl chloride. Therefore, AEGL-1 values were not recommended. In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to derive proposed AEGL-2 (1.0, 1.0, 0.83, 0.53, and 0.26 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) values for methanesulfonyl chloride. This approach was justified by the steep concentration-response curve (10% mortality in rats exposed to 20 ppm and 90% mortality at 28 ppm for 4-hr; Pennwalt Corporation, 1987). A 4-hour rat $BMCL_{05}$ of 15.5 ppm (Pennwalt Corporation, 1987) was used as the point-of-departure (POD) for the proposed AEGL-3 values (3.1, 3.1, 2.5, 1.6, and 0.78 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively). Values were scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. The 30-minute AEGL-3 value was proposed as the 10-minute value due to added uncertainty of extrapolating from the 4-hour POD to the 10-minute value. Uncertainty factors of 3 each were proposed for inter- and intraspecies variability because contact irritation is not expected to vary greatly between or within species. After discussion, a motion was made by Bob Benson and seconded by Calvin Willhite to derive AEGL-3 values as proposed except to use n=1 for time scaling, because log probit analysis of methanesulfonyl chloride rat lethality data ranging from 1 to 6 hours yielded a point estimate of n = 0.7, with lower and upper bounds of 0.3 and 1.1, respectively. Although, the model probability was low, the output of the log probit calculation excluded the default n = 3 for scaling from longer to shorter time points, and suggested that the n value is most likely around 1. The motion also included deriving AEGL-2 values by dividing the AEGL-3 values

by 3, and not recommending AEGL-1 values due to insufficient data. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix R).

Summary of AEGL Values for Methanesulfonyl chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	N R	NR	Not recommended
AEGL–2	4.0 ppm	4.0 ppm	2.1 ppm	0.53 ppm	0.26 ppm	One third the AEGL-3 values (NRC, 2001)
AEGL-3	12 ppm	12 ppm	6.2 ppm	1.6 ppm	0.78 ppm	4-hour rat $BMCL_{05}$ (Pennwalt Corporation, 1987).

Sulfuryl fluoride (CAS No. 2699-79-8)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Susan Ripple, Dow Chemical Company

Jennifer Rayner reviewed the data set and proposed AEGL values for sulfuryl fluoride (Attachment 14). Data were not sufficient to derive AEGL-1 values. Therefore, AEGL-1 values were not recommended. In the absence of empirical data and the presence of a steep dose response relationship (0% mortality at 404 ppm and 100% mortality at 603 ppm after 4 hour exposure, (Nitschke and Lomax 1989), the proposed AEGL-2 (37, 26, 20, 13, and 6.3 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) values were derived by dividing the proposed AEGL-3 values by 3 according to AEGL guidelines (NRC 2001). The proposed AEGL-3 values (110, 77, 61, 38, and 19 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were derived from the $BMCL_{05}$ of 383 ppm from Nitschke and Lomax (1989). Mice exposed to 603 ppm for four hours experienced 100% mortality within 5 days of exposure. An interspecies UF of 3 was proposed because a more sensitive species was used but the mechanism of action may differ among species. A 3 was proposed for intraspecies extrapolation to protect sensitive individuals. carbonyl fluoride has a steep concentration curve which may be indicative of small variation of toxic effects within a population. Values were scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. After discussion, a motion was made by Ernie Falke and seconded by Henry Anderson to base AEGL-3 values on a point-of-departure of 404 ppm for 4-hrs. This is the highest concentration showing no mortality in mice. A total uncertainty factor of 10 was applied to account for interspecies extrapolation (1) and intraspecies variability (10). A 1 was applied for interspecies extrapolation because the most sensitive species was used (mouse) and sulfuryl fluoride has a steep concentration-response curve. Time scaling used default exponent values of n = 1 or n = 3. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix S). A motion was then made by Richard Niemeier and seconded by Dieter Heinz to derive AEGL-2 values by dividing the AEGL-3 values by 3 and to adopt not recommended for AEGL-1. The motion passed (YES: 22; NO: 0; ABSTAIN: 0; Appendix S).

Summary of AEGL Values for Sulfuryl fluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	
AEGL–2	27 ppm	27 ppm	21 ppm	13 ppm	6.7 ppm	Reduction of AEGL-3 for steep dose response relationship (NRC 2001)
AEGL–3	81 ppm	81 ppm	64 ppm	40 ppm	20 ppm	Highest concentration with no lethality (Nitschke and Lomax 1989)

Carbonyl sulfide (CAS No. 463-58-1)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ralph Gingell, Shell Oil

Cheryl Bast reviewed the proposed AEGL values for carbonyl sulfide (Attachment 15). Proposed AEGL-1 values (26, 26, 23, 16, and 14 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a NOEL for all effects (150 ppm) in rats exposed for 6-hours (Morgan et al., 2004). An intraspecies UF of 3 was proposed and supported by the steep concentration-response curve. An interspecies UF of 3 was also proposed; although data suggested that the rat was not the most sensitive species, use of the default uncertainty factor of 10 would have yielded AEGL values inconsistent with the overall data base. Time scaling was proposed using an n value of 4.4. This exponent was derived from hydrogen sulfide rat lethality data and metabolism data suggest that the hydrogen sulfide metabolite may be responsible for the acute toxicity of carbonyl sulfide. Proposed AEGL-2 values (53, 53, 45, 33, and 28 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a NOEL for clinical signs and brain pathology in rats (300 ppm for 6-hr) (Morgan et al., 2004). Proposed AEGL-3 values were based on a 4-hour rat $BMCL_{05}/BMC_{01}$ of 952 ppm (Morgan et al., 2004). Uncertainty factor application and time scaling were proposed for AEGL-2 and AEGL-3 values as described above for AEGL-1. Discussion centered around the acceptability of data for AEGL-1 values and the selection of the time scaling exponent. There was concern that the hydrogen sulfide metabolite might not be the primary toxicant, and that, therefore, it is more appropriate to use the default time scaling exponents of n=1 or n =3. A motion was made by Dieter Heinz and seconded by John Hinz to adopt NR for AEGL-1 and to derive AEGL-2 values as proposed (POD and UF application) except to use default time scaling values of n= 1 or n =3. The motion passed (YES: 20; NO: 0; ABSTAIN: 1; Appendix T). A motion was then made by Bob Benson and seconded by Dieter Heinz to adopt AEGL-3 values as proposed except that default time scaling be used. The motion passed (YES: 19; NO: 0; ABSTAIN: 0; Appendix T).

Summary of AEGL Values for Carbonyl Sulfide						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	69 ppm	69 ppm	55 ppm	34 ppm	23 ppm	NOEL for clinical signs and brain pathology in rats (Morgan et al., 2004)
AEGL-3	190 ppm	190 ppm	150 ppm	95 ppm	48 ppm	4-hour rat $BMCL_{05}$ /BMC_{01}(Monsanto, 1985a)

2-Chloroethanol (CAS No. 107-07-3)

Staff Scientist: BobYoung, ORNL
Chemical Manager: George Rusch, Honeywell

Bob Young reviewed the data set for 2-chloroethanol (Attachment 16). AEGL-1 values were not recommended due to insufficient data. Proposed AEGL-2 values (11, 4.7, 3.2, 1.3, and 0.63 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were derived by dividing the proposed AEGL-3 values by 3. This approach was supported by a steep concentration-response relationship. Proposed AEGL-3 values (32, 14, 9.5, 3.8, and 1.9 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on experimental concentrations causing no death in rats exposed to 840 ppm for 15 minutes (10- and 30-min AEGL-3 values) or 226 ppm for 120 min (1-, 4-, and 8-hr AEGL-3 values) (Goldblatt et al., 1944). An interspecies UF of 3 was applied and was supported by rat and mouse lethality data. A default intraspecies UF of 10 was proposed and scaling across time was done by n=1 or n=3. After discussion, a motion was made by John Hinz and seconded by Dieter Hinz to base AEGL-3 values on a 120-minute nonlethal exposure at 280 ppm in mice (as an estimated lethality threshold). A 120-minute exposure to 1090 ppm resulted in 100% lethality. Uncertainty factor application and time scaling remained as proposed. Also included in the motion was to derive AEGL-2 values by dividing the AEGL-3 values by 3, and to adopt not recommended as the AEGL-1. The motion passed (YES: 18; NO: 0; ABSTAIN: 1; Appendix U).

Summary of AEGL Values for ethylene chlorohydrin *						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	insufficient data
AEGL-2	7.0 ppm	5.0 ppm	4.0 ppm	1.6 ppm	0.77 ppm	AEGL-2 values estimated as one third of the AEGL-3 values (NRC, 2001)
AEGL-3	21 ppm	15 ppm	12 ppm	4.7 ppm	2.3 ppm	Nonlethal exposure of mice to 280 ppm for 120 min. (Goldblatt, 1944)

*AEGL values for this chemical are slightly different than those shown on the ballot sheet due to a rounding error.

SPECIAL PRESENTATION

Toxicological Data Systems:
Dr. Gary Perlman (ATSDR, U.S. Public Health Service) presented information on toxicological data systems. Specifically, a hand held system that can be used in the field to access regulations and aid in emergency response was discussed. Dr. Perlman can be contacted for further information (Gap6@cdc.gov; Phone: 617-918-1492; FAX: 617-918-1494).

GENERAL ISSUES

ADMINISTRATIVE MATTERS

The next meeting of the NAC/AEGL will be held March 3-5, 2008, in Alexandria, VA.

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.

LIST OF ATTACHMENTS

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

Attachment 1. Meeting 44 agenda
Attachment 2. Meeting 43 attendee list
Attachment 3. MTBE Response to FR Comments
Attachment 4. Dimethylformamide Response to COT comments
Attachment 5. Agent VX New data Revisit
Attachment 6. Selected chlorosilanes presentation
Attachment 7. Carbonyl fluoride presentation
Attachment 8. Stibine presentation
Attachment 9. Boron tribromide presentation
Attachment 10. Chloropicrin presentation
Attachment 11. Methyl iodide presentation
Attachment 12. Allyl chloride presentation
Attachment 13. Methanesulfonyl chloridepresentation
Attachment 14: Sulfuryl fluoride presentation
Attachment 15: Carbonyl sulfide presentation
Attachment 16: 2-chloroethanol presentation

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Appendix B. Final NAC-43 Meeting Highlights
Appendix C. Ballot for chloropivaloyl chloride
Appendix D. Ballot for ethylene fluorohydrin
Appendix E. Ballot for thiophosgene
Appendix F. Ballot for MTBE
Appendix G. Ballot for n,n-dimethylformamide
Appendix H. Ballot for VX
Appendix I. Ballot for diethyldichlorosilane
Appendix J. Ballot for dimethylchlorosilane
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Appendix L. Ballot for methylvinyl dichlorosilane
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Appendix U. Ballot for 2-chloroethanol