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

September 6-8, 2006

Meeting-40 Highlights

Hyatt Regency-Bethesda
One Bethesda Metro Center (7400 Wisconsin Ave.)
Bethesda, MD 20814

INTRODUCTION

Chairman George Rusch welcomed the committee, and especially welcomed new NAC members Henry Anderson, Marc Baril, Alan Becker, Roberta Grant, Dieter Heinz, Elaine Kreuger, Daniel Sudakin, and Calvin Willhite.

The draft NAC/AEGL-39 meeting highlights were reviewed. Marc Ruijten pointed out that the AEGL-3 values for surfuryl chloride were incorrectly reported. The correct values are 14 ppm for 10- and 30-minutes, 11 ppm for 1-hour, 7.0 ppm for 4-hours, and 3.5 ppm for 8-hours. The ballot sheet from NAC-39 was consulted, and Marc's statement was verified. The NAC-39 minutes will be revised to reflect the correct AEGL-3 values for surfuryl chloride. A motion was made by John Hinz and seconded by Marc Ruijten to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-39 meeting highlights is attached (Appendix B).

The draft NAC/AEGL-37 meeting highlights were then reviewed; this meeting summary had not been previously reviewed due to human studies issues. A motion was made by George Rodgers and seconded by Bob Benson to accept the meeting highlights as presented. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-37 meeting highlights is attached (Appendix C).

The highlights of the NAC/AEGL-40 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-40 Agenda.

HUMAN STUDIES ISSUES

Oscar Hernandez, presented a synopsis of the EPA Final Rule on Protections for Subjects in Human Research regarding use of third party human pesticide data and the procedures to be used by the AEGL program to ensure consistency in application (Attachment 3). The Final Rule was published on February 6, 2006, and states that the EPA will not consider retrospective studies if there is "clear and convincing evidence that the conduct of the research was fundamentally unethical." The ORNL and EPA AEGL program staff scientists will complete ethics reviews of intentional human dosing studies used for development or support of Draft AEGL values, and the contents of these ethics reviews will be consistent with the ethics assessments performed by Office of Pesticide Programs (OPP) for submission to the Human Studies Review Board (HSRB). Ethics of any intentional dosing human studies added after Draft document status will be considered by the NAC/AEGL utilizing the SOP (p. 53) and recommendation 5-7 of the NAS report. Discussion focused on the definition of "harm", and whether or not the NAC/AEGL would be submitting studies to the HSRB (it will not).

REVISED AEGL CHEMICAL PRIORITY LIST: CHEMICAL CLASS FORMAT

Paul Tobin presented information regarding the revised chemical priority list and the chemical class system (Attachment 4). The presentation included an overview of AEGL definitions, uses of AEGLs, and how the chemical list is obtained. The grouping of chemicals by class has greatly improved efficiency of the AEGL process.

REVIEW of PRIORITY CHEMICALS

1,3,5-Trimethylbenzene (CAS No. 106-67-8)
1,2,4-Trimethylbenzene (CAS No. 95-63-6)
1,2,3-Trimethylbenzene (CAS No. 526-73-8)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: John Hinz, U.S. Air Force

Carol Wood summarized the data in the TSD (Attachment 5). Proposed AEGL-1 values (100 ppm for all time points) were based on slight eye and nose irritation in rats exposed to 1000 ppm for fifteen, 6-hour exposures (Gage, 1970). Values were held constant across time because minor irritation is not expected to vary with time, and inter- and intraspecies UFs of 3 each were proposed. Proposed AEGL-2 values (460 ppm for 10- and 30-min, 360 ppm for 1-hr, 230 ppm for 4-hr, and 150 ppm for 8-hr) were based on a threshold for AEGL-2 effects (eye and nose irritation, respiratory difficulty, lethargy, tremors, and decreased weight gain) in rats exposed to 2000 ppm for twelve, 6-hour exposures (Gage, 1970). Time scaling was accomplished using the default values of n =1 or n = 3; the 30-min value was adopted as the 10-min value, and inter- and intraspecies UFs of 3 each were proposed. Proposed AEGL-3 values (1100 ppm for 10-min, 790 ppm for 30-min, 630 ppm for 1-hr, 250 ppm for 4-hr, and 250 ppm for 8-hr) were based on no lethality and lateral position in mice exposed to 5000 ppm for 2-hours (Lazarew, 1929). Time scaling was accomplished using the default values of n =1 or n = 3;and inter- and intraspecies UFs of 3 each were proposed. Marc Ruijten expressed concern about using the Lazarew study for AEGL-3 derivation because of poor study quality (this study had previously been discarded for key study consideration in the hexane TSD). Concern was also raised regarding analytical techniques in the Gage (1970) study. A suggestion was made to better justify uncertainty factor selection for direct-acting irritancy and the argument that the three isomers are of similar toxicity. After further discussion, a motion was made by Calvin Willhite and seconded by John Hinz not to recommend AEGL-3 values because of insufficient data (no lethality below the saturated vapor concentration); to adopt the AEGL-2 values as proposed in the TSD, using the neurotoxicity data of Korsak (1995) as support. The motion also included a proposal to adopt AEGL-1 values of 180 ppm for 10- and 30-min, 140 ppm for 1-hr, 90 ppm for 4-hr, and 45 ppm for 8-hr based on mild neurotoxic effects in rats at 900 ppm (average of EC_{50} concentrations for the three isomers) for 4-hours (Korsak, 1995). Time scaling was accomplished using the default values of n =1 or n = 3; the 30-min value was adopted as the 10-min value, and inter- and intraspecies UFs of 3 each were applied. The motion carried (AEGL-1: YES: 20; NO: 1; ABSTAIN: 0) (AEGL-2 and AEGL-3: YES: 21; NO: 0; ABSTAIN: 0). (APPENDIX D).

Summary of AEGL Values for 1,3,5-Trimethylbenzene; 1,2,4-Trimethylbenzene; and 1, 3, 5-Trimethylbenzene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	180 ppm	180 ppm	140 ppm	90 ppm	45 ppm	Mild neurotoxicity in rats (Korsak, 1995)
AEGL–2	460 ppm	460 ppm	360 ppm	230 ppm	150 ppm	Threshold for AEGL-2 effects (eye and nose irritation, respiratory difficulty, lethargy, tremors, and decreased weight gain) in rats (Gage, 1970)
AEGL–3	NR	NR	NR	NR	NR	Not recommended: Insufficient data

Ethylene Oxide (CAS No. 75-21-8)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Susan Ripple, chemical manager, made a few introductory remarks about the issues regarding ethylene oxide, and why it has been under discussion for 10 years. The discussion will be limited to AEGL-2, and issues include use of developmental toxicity data in mice. The developmental toxicity studies are repeated-exposure by design and the mouse is not the best surrogate for humans. Kowetha Davidson then explained that a more appropriate approach for derivation of AEGL-2 values for ethylene oxide is to use recently-available acute neurotoxicity data in rats (Attachment 6). Proposed AEGL-2 values (80 ppm for 10- and 30-min, 45 ppm for 1-hr, 14 ppm for 4-hr, and 7.9 ppm for 8-hr) were based on a NOAEL for neurotoxicity in rats exposed to 100 ppm ethylene oxide for 6 hours (Mandella, 1997). Proposed time scaling used the equation $c^n \times t = k$, where n = 1.2 as determined from empirical LC_{50} data for the rat for 1 and 4 hours; the 30-minute value was adopted as the 10-minute value. An interspecies uncertainty factor of 3 was proposed because one potential mechanism of toxicity (direct DNA and protein alkylation) is not expected to differ between species, neurotoxic endpoints are similar in rats and humans, PBPK modeling indicates little difference between rats and humans for AUC and dose/mg/kg bw. An intraspecies uncertainty factor of 3 was also proposed because glutathione-S-transferase polymorphism can modulate systemic exposure as measured by hemoglobin adducts but appears to be within a factor of 3 in the population. Several committee members suggested explaining in the TSD why the BMC approach was not used. George Woodall then presented different approaches for calculation of the time-scaling exponent, n (Attachment 7). He explained that other options included using data from Nachreiner (1991, 1992) to derive a value of n = 1.4 or data from Weller (1991) to derive a value of n = 1.7. Bill Snellings then explained that the Weller study had limitations (mice died in the control group, some animals were pregnant and some were

not, methods were not completely reported, and the study was not GLP) and should not be used for derivation of n for time scaling. After discussion, a motion was made by John Hinz and seconded by Richard Thomas to accept the AEGL-2 values as proposed. The motion carried (YES: 17; NO: 1; ABSTAIN: 2) (APPENDIX E).

Summary of AEGL-2 Values for Ethylene Oxide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–2	80 ppm	80 ppm	45 ppm	14 ppm	7.9 ppm	NOAEL for neurotoxicity in rats (Mandella, 1997)

Trifluorochloroethylene (CAS No.79-38-9)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: George Rusch, Honeywell

Sylvia Talmage presented an overview of the TSD for trifluorochloroethylene and the derivation of the draft AEGL values (Attachment 8). Following a brief discussion, a motion was made by Susan Ripple and seconded by Dieter Heinz to accept the AEGL values as proposed. AEGL-1 values: 29 ppm, 20 ppm, 16 ppm, 10 ppm, and 10 ppm; AEGL-2 values: 160 ppm, 110 ppm, 86 ppm, 54 ppm, 54 ppm, and AEGL-3 values: 360 ppm, 250 ppm, 200 ppm, 130 ppm, 100 ppm. The motion passed (AEGL-1: YES: 13; NO: 5; ABSTAIN: 2) (AEGL-2: YES:14; NO: 4; ABSTAIN: 2) (AEGL-3: YES: 11; NO: 4; ABSTAIN: 4). (APPENDIX F). In response to a request by the Chairman for why some members did not approve the values revealed concerns about the uncertainty factors, especially with respect to people with renal deficiencies. Following additional discussion, it was decided that Marc Ruitjen would further analyze data from a German study (Walther and Fischer, 1968) for possible application in the derivation of alternate AEGL-3 values. Later in the meeting, it was the consensus of the NAC/AEGL to re-open discussions on AEGL-3 values. In order to develop an n value from the empirical data of Walther and Fischer (1968), Marc applied a tenBerge computer program that integrates all partial lethality data for various exposure durations. Exposure durations greater than 8 hours were excluded. The resulting n value was 1.37, and resulting AEGL-3 values were 1500 ppm for 10-minutes, 690 ppm for 30-minutes, 420 ppm for 1-hour, 150 ppm for 4-hours, and 91 ppm for 8-hours (Attachment 8a). Additional discussion resulted in approval (motion made by Marc Ruitjen and seconded by Dieter Heinz; vote: YES: 14; NO: 3; ABSTAIN: 2) (APPENDIX F) of this new set of AEGL-3 values.

Summary of AEGL Values for Trifluorochloroethylene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	29 ppm	20 ppm	16 ppm	10 ppm	10 ppm	NOAEL for kidney effects - rat (Potter et al. 1981)
AEGL–2	160 ppm	110 ppm	86 ppm	54 ppm	54 ppm	Reversible kidney lesions - rat (Potter et al. 1981)
AEGL–3	1500 ppm	690 ppm	420 ppm	150 ppm	91 ppm	Mouse lethality data (Walther and Fischer, 1968)

Hexafluoropropylene (CAS No. 116-15-4)

Staff Scientist:, Bob Young, ORNL
Chemical Manager: George Rusch, Honeywell

Robert Young presented a summary of the available data and an overview of the development of proposed AEGL value for hexafluoropropylene (HFP) (Attachment 9). For AEGL-1 values there was discussion regarding the use of an interspecies uncertainty factor of 10 rather than 3. It was agreed that an interspecies uncertainty factor of 3 was appropriate because the effects of HFP for a given exposure concentration appeared to be similar among the species tested. It was also agreed that the 10-minute value would be time-scaled using the empirically-derived *n* of 1.33 for the equation $C^n \times t = k$ rather than set equivalent to the 30-minute value (the POD was based on a 4-hour experimental exposure duration and the value of *n* was calculated using experimental exposure durations ranging from 30 to 480-minutes). Based upon a no-effect POD (no effects in rats exposed to 140 ppm HFP for 4 hrs, Du Pont & Co., 1960) and because the continuum of HFP-induced mild effects is not likely to vary considerably among individuals, the intraspecies uncertainty factor was also limited to 3. A motion to accept the modified AEGL-1 values (150 ppm, 67 ppm, 40 ppm, 14 ppm, and 8.3 ppm for 10 min, 30 min, 1 hr, 4 hrs and 8 hrs) was made by Marc Ruijten and seconded by Richard Thomas; the motion passed unanimously (YES: 22; NO: 0; ABSTAIN: 0) (APPENDIX G). The AEGL-2 values were based upon reversible nephrosis and altered renal function in rats exposed to 320 ppm HFP for 4 hours (Du Pont & Co., 1960). As for the AEGL-1 values, it was the consensus of the NAC/AEGL that the 10-minute AEGL-2 value be derived using time scaling rather than set equivalent to the 30-minute value. The uncertainty factors of 3 (interspecies) and 3 (intraspecies) were again considered appropriate. A motion by Henry Anderson (seconded by Bob Benson) to accept the AEGL-2 values of 350 ppm, 150 ppm, 91 ppm, 32 ppm, and 19 ppm for 10 min, 30 min, 1, 4, and 8 hrs, passed

unanimously (YES: 22; NO: 0; ABSTAIN: 0) (APPENDIX G). The AEGL-3 values were based upon a 4-hr $BMCL_{05}$ for lethality in rats (Du Pont & Co., 1960). Because the rat appeared to be a more sensitive species and because 4-hr LC_{50} values varied about 4-fold among four species, the interspecies uncertainty factor was limited to 3. An intraspecies uncertainty factor of 3 accounted for possible variability in metabolism-mediated formation of toxic intermediates from the metabolism of HFP. The AEGL-3 values of 1800 ppm 800 ppm, 480 ppm, 170 ppm, and 100 ppm for 10 min, 30 min, 1, 4, and 8 hrs passed unanimously (YES: 22; NO: 0; ABSTAIN: 0) (APPENDIX G) (motion by Bob Benson, seconded by John Hinz).

Summary of AEGL Values for Hexafluoropropylene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	150 ppm 920 mg/m^3	67 ppm 410 mg/m^3	40 ppm 240 mg/m^3	14 ppm 85 mg/m^3	8.3 ppm 51 mg/m^3	Absence of notable toxic effects in rats exposed to 140 ppm HFP for 4 hrs (Du Pont & Co., 1960)
AEGL–2	350 ppm 2100 mg/m^3	150 ppm 920 mg/m^3	91 ppm 560 mg/m^3	32 ppm 200 mg/m^3	19 ppm 120 mg/m^3	Reversible nephrosis and altered renal function in rats exposed to 320 ppm HFP for 4 hrs. (Du Pont & Co., 1960)
AEGL–3	1800 ppm 11,000 mg/m^3	800 ppm 4900 mg/m^3	480 ppm 2900 mg/m^3	170 ppm 1000 mg/m^3	100 ppm 600 mg/m^3	Rat $BMCL_{05}$ of 1677 ppm HFP, 4 hr exposure (Du Pont & Co., 1960)

Tetrafluoroethylene (CAS No. 116-14-3)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: George Rusch, Honeywell

An overview of the available data and the derivation of draft AEGL values was provided by Sylvia Talmage of Oak Ridge National Laboratory (Attachment 10). For the AEGL-1, the NOAEL of 1200 ppm for renal effects in rats and mice exposed for 6 hours was considered an appropriate critical effect and POD. The total uncertainty factor application was 10 (3 for interspecies variability and 3 for individual variability). The AEGL values with the 10-minute value being set equivalent to the 30-minute value) of 270 ppm, 270 ppm, 220 ppm, 140 ppm, and 90 ppm were approved by the NAC (motion by George Rodgers, seconded by Marc Baril) (YES: 19; NO:0; ABSTAIN: 1) (APPENDIX H). The AEGL-2 values, their critical effect (changes in renal clinical chemical indices in the rat following exposure of 3000 ppm for 6 hours) and uncertainty factor application (total UF of 10 as for AEGL-1 values) were accepted with the 10-minute value being set equivalent to the 30-minute value (690 ppm. 690 ppm, 550 ppm, 340 ppm,

230 ppm; motion by Bob Benson, seconded by Steve Barbee) (YES: 20; NO:0; ABSTAIN: 2) (APPENDIX H). It was requested to incorporate verbiage in appropriate sections of the TSD regarding the data showing that the next higher exposure in the Odum and Green (1984) study resulted in irreversible effects. Discussions on the AEGL-3 values focused on use of the $BMCL_{05}$ value from hamster data (DuPont, 1980) as the POD. During the discussion, the use of the restricted slope function and data exclusion/inclusion arose. Review and report regarding these was noted as an Action Item (Woodall, Falke, Camacho) for the next NAC/AEGL meeting. The resulting AEGL-3 values of 4200 ppm, 4200 ppm, 3300 ppm, 2100 ppm, and 1000 ppm (total UF of 3 x 3) based upon the $BMCL_{05}$ from the hamster data were approved (motion by Bob Benson, seconded by George Rodgers) (YES: 20; NO:0; ABSTAIN: 2) (APPENDIX H).

Summary of AEGL Values for Tetrafluoroethylene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	270 ppm	270 ppm	220 ppm	140 ppm	90 ppm	No adverse renal effects in rats and mice; 1200 ppm, 6 hrs, UF=3x3 (Keller et al.,2000)
AEGL–2	690 ppm	690 ppm	550 ppm	340 ppm	230 ppm	Changes in urinary clinical chemistry indices- rat; 3000 ppm, 6 hrs; UF=3x3 (Odum and Green, 1984)
AEGL–3	4200 ppm	4200 ppm	3300 ppm	2100 ppm	1000 ppm	$BMCL_{05}$ hamster (DuPont, 1980)

Ethyl Benzene (CAS No.100-41-4)

Staff Scientist:Carol Wood, ORNL
Chemical Manager: John Hinz, U.S. Air Force

Carol Wood reviewed the data set for ethyl benzene (Attachment 11). Dr. Marcy Banton, Lyondell Chemical, explained the availability of new unpublished industry data that may affect the derivation of AEGL values for ethyl benzene. The discussion of this chemical was postponed pending evaluation of these new data.

SELECTED CHLOROFORMATES

Phenyl Chloroformate (CAS Reg. No. 185-14-9)
2-Ethylhexyl Chloroformate (CAS Reg. No.24468-13-1)

Benzyl Chloroformate (CAS Reg. No. 501-53-1)

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

Overview

Cheryl Bast thanked Dr. Roland Rossbacher, representing BASF, Germany, for providing unpublished industry data on the chloroformates. These data were used as key and supporting studies for many of the chloroformates. Cheryl then discussed the overall data set available for the chloroformates (Attachment 12), and explained that the three chloroformates under consideration at NAC-40 will be included in the TSD with the chloroformates discussed at NAC-39. Although data sets for individual chloroformates are sparse, the total data set for all chloroformates helped increase confidence in the derived AEGL values. All of the title chloroformates are direct-acting contact irritants and are corrosive to the eyes, skin, gastrointestinal, and respiratory tracts. Therefore, when AEGL values were derived, uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation (total UF = 10). Time scaling for all chloroformates was done using the default values of n =1 (shorter-to- longer time) or n =3 (longer-to-shorter time), because data were not sufficient to derive chemical-specific exponents. Summaries of AEGL development for the title chloroformates are provided below.

Phenyl Chloroformate

AEGL-1 values for phenyl chloroformate were not recommended due to insufficient data. Proposed AEGL-2 values (0.24 ppm for 10-min, 0.24 ppm for 30-min, 0.19 ppm for 1-hr, 0.12 ppm for 4-hr, and 0.06 ppm for 8-hr) were derived by dividing the AEGL-3 values by 3. This approach is justified based on a steep concentration-response curve. Proposed AEGL-3 values (0.72 ppm for 10-min, 0.72 ppm for 30-min, 0.57 ppm for 1-hr, 0.36 ppm for 4 -hr, and 0.18 ppm for 8-hr) were based on a 4-hr $BMCL_{05}$ in rats of 3.6 ppm (BASF, 1990; Hoechst, 1989). Uncertainty factor application and time scaling were applied as discussed above in the overview section. After discussion, a motion was made by George Rodgers and seconded by Dieter Heinz to accept the AEGL values as proposed. The motion carried (YES: 18; NO: 0; ABSTAIN: 2) (APPENDIX I).

Summary of AEGL Values for Phenyl Chloroformate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.06 ppm	1/3 the AEGL-3 values

AEGL-3	0.72 ppm	0.72 ppm	0.57 ppm	0.36 ppm	0.18 ppm	4-hr $BMCL_{05}$ in rats (BASF, 1990; Hoechst, 1989)

2-Ethylhexyl Chloroformate

AEGL-1 values for 2-ethylhexyl chloroformate were not recommended due to insufficient data. Proposed AEGL-2 values (1.2 ppm for 10-min, 1.2 ppm for 30-min, 0.97 ppm for 1-hr, 0.60 ppm for 4 -hr, and 0.30 ppm for 8-hr) were derived by dividing the AEGL-3 values by 3. This approach is justified based on a steep concentration-response curve. Proposed AEGL-3 values (3.6 ppm for 10-min, 3.6 ppm for 30-min, 2.9 ppm for 1-hr, 1.8 ppm for 4 -hr, and 0.91 ppm for 8-hr) were based on a 4-hr $BMCL_{05}$ in rats of 18.1 ppm (BASF, 1985). Uncertainty factor application and time scaling were applied as discussed above in the overview section. After discussion, a motion was made by George Rodgers and seconded by Dieter Heinz to accept AEGL-1, AEGL-2, and AEGL-3 values as proposed. The motion carried (YES: 18; NO: 0; ABSTAIN: 2) (APPENDIX J).

Summary of AEGL Values for 2-Ethyl hexyl Chloroformate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	1.2 ppm	1.2 ppm	0.97 ppm	0.60 ppm	0.30 ppm	1/3 the AEGL-3 values
AEGL-3	3.6 ppm	3.6 ppm	2.9 ppm	1.8 ppm	0.91 ppm	4-hr $BMCL_{05}$ in rats (BASF, 1985)

Benzyl Chloroformate

AEGL-1 values for benzyl chloroformate were not recommended due to insufficient data. Proposed AEGL-2 values (1.2 ppm for 10-min, 1.2 ppm for 30-min, 0.97 ppm for 1-hr, 0.63 ppm for 4 -hr, and 0.31 ppm for 8-hr) were derived by dividing the AEGL-3 values by 3. This approach is justified based on a steep concentration-response curve. Proposed AEGL-3 values (3.7 ppm for 10-min, 3.7 ppm for 30-min, 2.9 ppm for 1-hr, 1.9 ppm for 4 -hr, and 0.93 ppm for 8-hr) were based on a concentration causing no mortality in rats exposed to benzyl chloroformate for 4 hours (18.6 ppm) (BASF, 1990). Uncertainty factor application and time scaling were applied as discussed above in the overview section. After discussion, a motion was made by George Rodgers and seconded by Dieter Heinz to accept AEGL-1, AEGL-2, and AEGL-3 values as proposed. The motion carried (AEGL-1: YES: 18; NO: 1; ABSTAIN: 1) (APPENDIX K).

Summary of AEGL Values for Benzyl Chloroformate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	1.2 ppm	1.2 ppm	0.97 ppm	0.63 ppm	0.31 ppm	1/3 the AEGL-3 values
AEGL-3	3.7 ppm	3.7 ppm	2.9 ppm	1.9 ppm	0.93 ppm	No death in rats (4-hr) (BASF, 1990)

Summary: The analysis presented comparing the relative toxicity of the chloroformates vs. the derived AEGL values will be revised by removing RD50 data before presentation to the COT subcommittee. Also, more information on hydrolysis products and production data. Also, Marc Ruijten may have another approach for derivation of AEGL-2 values for chloroformates previously addressed at NAC-39 (not NAC-40 chemicals). Marc will provide comments regarding these potential AEGL-2 derivations to Ernest Falke and Cheryl Bast so that the issue may be addressed at NAC-40, if necessary.

Dibromoethane (CAS No. 106-93-4)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Bob Benson, the Chemical Manager, provided an introductory discussion of previous NAC action on this chemical. The TSD for Dibromoethane was first reviewed during NAC-34 (September 2004). At that time Kowetha Davidson was the ORNL Staff Scientist and Nancy Kim, NY State Department of Health, was the Chemical Manager. At the meeting the NAC accepted AEGL-3 values calculated by Marc Ruitjen using an alternate form of the ten Berge equation. Discussion of AEGL-2 values was deferred as the values in the TSD were developed from a developmental toxicity study reported in an abstract only. For reasons which are unclear, the TSD was not brought back to the NAC until this meeting. During preparation of the revised TSD, it was discovered that the calculation of the previous AEGL-3 values could not be repeated because of data entry errors. In addition it was learned that the group who conducted the developmental toxicity study did not intend to publish the data. Therefore, a new TSD was developed for consideration by the NAC.

Kowetha Davidson presented a summary of the data in the TSD (Attachment 13). The primary data used for development of all AEGL values come from series of studies by Rowe et al. (1952). The study contained information on lethality, as well as data on toxic effects to internal organs at non-lethal exposures. After the presentation by Kowetha Davidson, it was moved by Mark Ruitjen and seconded by Bob Benson to withdraw the previously adopted AEGL-3 values. The motion was unanimously accepted by the NAC. It was

moved by Bob Benson and seconded by Calvin Willhite to accept the AEGL-1 values in the TSD. The basis was the no effect level for mild histopathological lesions in the liver observed at an exposure of 50 ppm for 420 minutes with n = 1.6, an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 10. The value of n was based on time course data in Rowe et al. (1952) for no effect levels and effect levels for liver effects at exposures ranging from 6 minutes to 7 hours. An interspecies uncertainty factor of 1 was used as pharmacokinetic modeling (Hissink et al., 2000) showed that humans would be much less sensitive to the toxic effects than rats. The values are 10 minutes, 52 ppm; 30 minutes, 26 ppm; 1 hour, 17 ppm; 4 hours, 7.1 ppm; and 8 hours, 4.6 ppm. The motion passed (YES, 15; NO: 0; ABSTAIN: 2) (APPENDIX L).

It was then moved by Calvin Willhite and seconded by Dieter Heinz to accept the AEGL-2 values in the TSD. The basis was the effect level for mild histopathological lesions in the liver observed at an exposure of 100 ppm for 240 minutes with n = 1.6, an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 10. This exposure was considered as the no effect level for irreversible toxicity. The rationale for n and the uncertainty factors was the same as for AEGL-1. The motion passed (YES:16; NO: 1; ABSTAIN: 2) (APPENDIX L).

It was moved by Bob Benson and seconded by Calvin Willhite to accept the AEGL-3 values in the TSD. The basis was the no effect level for lethality (LC_{01}) at 100 ppm following an exposure of 8.5 hours. The value of n was 1.4 based on regression of LC_{01} values for exposures ranging from 6 to 120 minutes. The rationale for the uncertainty factors was as for AEGL-1 and AEGL-2. The values are 10
minutes, 170 ppm; 30 minutes, 76 ppm; 1 hour, 46 ppm; 4 hours, 17 ppm; and 8 hours, 10 ppm). The motion passed (YES: 15; NO, 3; ABSTAIN: 2) (Appendix L). Several members also made suggestions for editorial changes to the TSD.

Summary of AEGL Values for Dibromoethane

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	52 ppm	26 ppm	17 ppm	7.1 ppm	4.6 ppm	NOEL in rats (Rowe et., 1952)
AEGL–2	73 ppm	37 ppm	24 ppm	10 ppm	6.5 ppm	Slight liver histopathology in rats (Rowe et al., 1952)
AEGL-3	170 ppm	76 ppm	46 ppm	17 ppm	10 ppm	8.5-hr LC_{01} in rats (Rowe et al., 1952)

Propargyl alcohol (CAS No. 107-19-7)

Staff Scientist:, Bob Young, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Discussion of the propargyl alcohol TSD was deferred to NAC-41 so that unpublished industry data (BASF) could be obtained and included in the TSD.

Phenyl Mercaptan (CAS No. 108-98-5)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Steve Barbee, Arch Chemical

Cheryl Bast reviewed the data set for phenyl mercaptan (Attachment 13). AEGL-1 values were not recommended due to insufficient data. No robust data consistent with the definition of AEGL-2 were available. Therefore, proposed AEGL-2 values (1.0 ppm for 10-min, 0.70 ppm for 30-min, 0.53 ppm for 1-hr, 0.33 ppm for 4-hr, and 0.17 ppm for 8-hr) were based upon a 3-fold reduction in the AEGL-3 values; this approach was considered appropriate because of the steep concentration-response curve. Proposed AEGL-3 values (3.0 ppm for 10-min, 2.1 ppm for 30-min, 1.6 ppm for 1-hr, 1.0 ppm for 4-hr, and 0.52 ppm for 8-hr) were based on a calculated LC_{01} (10.3 ppm) in rats exposed to phenyl mercaptan for 4 hours (Fairchild and Stokinger, 1958). Intraspecies and interspecies uncertainty factors of 3 each were proposed. Time scaling was done using the default values of n =1 (shorter-to- longer time) or n =3 (longer-to-shorter time), because data were not sufficient to derive chemical-specific exponents. Time scaling from the 4-hour point-of-departure to the 10-minute AEGL-3 value was supported by 1-hour rat lethality data (Stauffer Chemical Company, 1969). After discussion, a motion was made by John Hinz and seconded by Susan Ripple not to recommend AEGL-1 values. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX M). A motion was then made by George Rodgers and seconded by Marc Ruijten to adopt AEGL-3 values as proposed. This motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX M). A motion was then made by Steve Barbee and seconded by Dieter Heinz to adopt AEGL-2 values as proposed. The motion carried (YES: 16; NO: 1; ABSTAIN: 0) (APPENDIX M). Suggestions for document revision included indicating that there are no data for LOA calculation and adding a table of relative toxicity of hydrogen sulfide and other mercaptans. A suggestion was also made to present options for UF justification to the COT subcommittee showing the current approach or using a factor to adjust the derived AEGL values.

Summary of AEGL Values for Phenyl Mercaptan						
Classification	**10-minutes**	**30-minutes**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	1.0 ppm	0.70 ppm	0.53 ppm	0.33 ppm	0.17 ppm	3-fold reduction of AEGL-3 values
AEGL-3	3.0 ppm	2.1 ppm	1.6 ppm	1.0 ppm	0.52 ppm	LC_{01} in rats (Fairchild and Stokinger, 1958)

GENERAL ISSUES

The following general issues emerged from the meeting:

TSDs should include a section on combustion products if available.

If possible, set up a docket to allow for timely industry input for future chemicals.

Renal sensitivity for trifluorochloroethylene, hexafluorofluoropropylene, and tetrafluoroethylene should be evaluated to determine if an intraspecies uncertainty factor of 3 is justifiable.

Tetrafluoroethylene and vinyl chloride should be evaluated by the COT subcommittee concurrently (cancer assessment).

The restricted slope issue from the benchmark dose software should be examined (George Woodall, Ernie Falke, Iris Camacho).

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-41: December 12-14, 2006, Washington DC
NAC/AEGL-42: March 20-22, 2007, Irvine, CA
NAC/AEGL-43: June 19-21, 2007, Netherlands (?)

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, and Robert Benson, U.S. EPA, with input from the respective staff scientists, chemical managers, and other contributors.

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-40 Meeting Agenda
Attachment 2. NAC/AEGL-40 Attendee List
Attachment 3. Protections for Subjects in Human Research- Current Procedures for the AEGL Program
Attachment 4. Revised AEGL Chemical Priority List: Chemical Class System
Attachment 5. Data analysis for trimethylbenzenes
Attachment 6. Data analysis for ethylene oxide
Attachment 7. Considerations for deriving a value of n for ethylene oxide
Attachment 8. Data analysis for trifluorochloroethylene
Attachment 8a. Analysis of Walther and Fischer data for trifluorochloroethylene
Attachment 9. Data analysis for hexafluoropropylene
Attachment 10. Data analysis for tetrafluoroethylene
Attachment 11. Data analysis for ethyl benzene
Attachment 12: Data analysis for selected chloroformates
Attachment 13: Data analysis for selected dibromoethane
Attachment 14: Data analysis for phenyl mercaptan

LIST OF APPENDICES

Appendix A. Ballot for NAC-37 and NAC-39 meeting summary
Appendix B. Final NAC-39 Meeting Highlights
Appendix C. Final NAC-37 Meeting Highlights
Appendix D. Ballot for trimethyl benzenes
Appendix E. Ballot for ethylene oxide
Appendix F. Ballot for trifluorochloroethylene
Appendix G. Ballot for hexafluoropropylene
Appendix H. Ballot for tetrafluoroethylene
Appendix I. Ballot for phenyl chloroformate
Appendix J. Ballot for 2-ethylhexyl chloroformate
Appendix K. Ballot for benzyl chloroformate
Appendix L. Ballot for dibromoethane
Appendix M. Ballot for phenyl mercaptan
Appendix N. Committee chairman certification of minutes