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

June 13-15, 2005

Final Meeting-37 Highlights

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., N.W.
Washington, DC 20210

INTRODUCTION

Chairman George Rusch welcomed the committee. Sharon Frazier was introduced to the Committee and spoke about travel procedures, including travel authorizations and vouchers. Ernest Falke announced that the next NAS/COT Subcommittee meeting (NAS-16) will be August 31 and September 1-2, 2005, in Woods Hole MA. The next NAC meeting (NAC-38) will be September 28-30, 2005, in Washington, D.C.

The draft NAC/AEGL-36 meeting highlights were reviewed. Marc Ruijten stated that he obtained raw data for MTBE from Dr. ten Berge, not LC_{01} data as stated in the draft highlights. He also stated that, in his opinion, AEGL values should not have been developed for nitrogen mustards due to the sparse data base. Bob Benson requested that the Point-of-departure discussion be clarified for hexafluoroacetone. George Woodall stated that he had provided uncertainty factor database information to Iris Camacho. John Morawetz will work with Kowetha Davidson to clarify the human study descriptions for peracetic acid. Mr. Morawetz also had suggestions regarding AEGL definitions on the web site. These suggestions were incorporated into the highlights. A motion was made by Nancy Kim and seconded by John Hinz to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-36 meeting highlights is attached (Appendix B).

The highlights of the NAC/AEGL-37 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-37 Agenda.

STATUS REPORT OF UNCERTAINTY FACTOR ANALYSIS

Iris Camacho provided information on the status of the Uncertainty Factor analysis (Attachment 3). A database has been created using information provided by chemical managers. George Rusch encouraged chemical managers who had not yet provided information to do so in a timely manner so that the database work may progress. Dr. Camacho informed the NAC that the database will be distributed to committee members when it is complete.

SOP PBPK White Paper

Jim Dennison discussed revisions to the PBPK white paper. There were two issues: (1) workload, and (2) UF application. Dr. Dennison said that workload could affect CNS depressants (e.g. xylenes) 2-4 fold. He mentioned that AEGLs for resting and workload conditions would be provided to the NAC members to help them in the UF selection. He also indicated that the white paper has taken a flexible approach. Marc Ruijten liked the idea that the current version of the PBPK white paper gives flexibility. He liked the initial option of the default approach and flexibility to deviate from it. Tom Hornshaw was concerned that the NAC committee did not have the technical expertise to run the PBPK models. Regarding the issue on the selection of UFs, the white paper proposes to apply UFs to the dosimetric as the default option, but if need be, modeler can deviate from this approach. George Woodall suggested that TSD should capture the variability of the parameters (input, etc.) so the process is more transparent. A motion was made by Susan Ripple and seconded by George Woodall to send the white paper to the COT Subcommittee. The motion carried (YES:16; NO: 0; ABSTAIN: 1) (Appendix C).

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS ON INTERIM AEGL VALUES

Sulfur Dioxide (CAS No. 7446-09-5)

Chemical Manager: George Woodall, U.S. EPA
Staff Scientist: Cheryl Bast, ORNL

Cheryl Bast discussed the data set and COT/AEGL's comments (Attachment 4). The COT/AEGL suggested that the AEGL-1 and AEGL-2 values be revised to be more protective of asthmatic humans. The originally derived AEGL-1 value was 0.25 ppm across all time points; the POD was a weight-of-evidence approach showing mild bronchoconstriction in exercising asthmatics. The COT/AEGL suggested that the value be revised to 0.20 ppm across all time points, because moderate bronchoconstriction was noted in one study at 0.25 ppm with low humidity. The originally derived AEGL-2 values were 1.0 ppm for 10-min, 30-min, and 1-hr, and 0.75 ppm for 4- and 8-hours based on a weight-of-evidence approaching showing moderate to severe, but reversible respiratory responses in asthmatics at 1.0 ppm for up to 40 minutes

exposure. The COT/AEGL suggested that the value be revised to 0.75 ppm across all time points, as a NOEL for severe bronchoconstriction. After discussion, a motion was made by Steve Barbee and seconded by John Hinz to adopt AEGL-1 and AEGL-2 values as proposed. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (APPENDIX D).

Summary of AEGL Values for Sulfur Dioxide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	NOEL for bronchoconstriction in exercising asthmatics (weight of evidence)
AEGL–2	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	0.75 ppm	NOEL for severe bronchoconstriction in exercising asthmatics (weight of evidence)

Chloroform(CAS No. 67-66-3)

Chemical Manager: Steve Barbee, Arch Chemicals
Staff Scientist: Bob Young, ORNL

Bob Young discussed the data set and COT/AEGL's comments (Attachment 5). The COT/AEGL concurred with the AEGL-1 and AEGL-2 values for chloroform, but was concerned that the AEGL-3 values were overly conservative. A PBPK model suggests that the rate of chloroform metabolism in mice is 25-50x greater than humans; therefore, the interspecies UF is likely <1. No data exist to decrease intraspecies UF to less than 3. Therefore, Bob Young proposed using a weight-of-evidence factor of 1/3 to account for rodent/human metabolism and dosimetry differences. After much discussion, a motion was made by Bob Benson and seconded by John Hinz to adopt AEGL-3 values of 4000 ppm for 10- and 30-minutes, 3200 ppm for 1 hour, 2000 ppm for 4 hours, and 1600 ppm for 8 hours. The point-of-departure is an estimated threshold for lethality in mice (540 minute LC_{50} of 4500 ÷ 3 = 1500 ppm) (Gehring, 1968). Time scaling was accomplished using default values of n =1 or n =3. An interspecies UF of 1, intraspecies UF of 3, and modifying factor of 1/3 were proposed. The motion carried (YES: 14; NO: 0; ABSTAIN: 3) (APPENDIX E).

Summary of AEGL Values for Chloroform						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–3	4000 ppm	4000 ppm	3200 ppm	2000 ppm	1600 ppm	Estimated lethality threshold in mice (Gehring, 1958)

Carbon Tetrachloride (CAS No. 56-23-5)

Chemical Manager: Bill Bress, Vermont
Staff Scientist: Robert Young, ORNL

Bob Young discussed the data set and COT/AEGL's comments (Attachment 6). The COT/AEGL was concerned that the AEGL-1, AEGL-2, and AEGL-3 values were overly conservative due to the use of excessive uncertainty factors. Dr. Young proposed developing AEGL-1 values of 58 ppm for 10- and 30-minutes, 44 ppm for 1 hour, 25 ppm for 4 hours, and 19 ppm for 8 hours. based on no CNS or renal effects in humans exposed to 76 ppm for 4-hours (Davis, 1934) and applying an intraspecies UF of 3. Proposed AEGL-2 values of 380 ppm for 10-minutes, 250 ppm for 30-minutes, 190 ppm for 1 hour, 100 ppm for 4 hours, and 81 ppm for 8 hours were based on nausea, vomiting, and headache in humans exposed to 1191 ppm for 9 minutes (Davis, 1934). An intraspecies UF of 3 was applied. Proposed AEGL-3 values of 1000 ppm for 10-minutes, 690 ppm for 30-minutes, 500 ppm for 1 hour, 300 ppm for 4 hours, and 230 ppm for 8 hours were based on a 1-hour LC_{01} value in rats (Adams et al., 1952; Dow Chemical, 1986). An intraspecies UF of 10, interspecies UF of 3, and weight-of-evidence factor of 1/3 were proposed. After a lengthy discussion, a motion was made by Ernie Falke and seconded by Bill Bress to accept the revised values as proposed with the exception of applying an interspecies UF of 1 and intraspecies UF of 10 (supported by human P450 data) for the AEGL-3 derivation. Also, the monkey repeated-exposure data will be used as support for AEGL-1 values. The motion carried (YES: 11; NO: 3; ABSTAIN: 3) (APPENDIX F).

Summary of AEGL Values for Carbon Tetrachloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	58 ppm	58 ppm	44 ppm	25 ppm	19 ppm	NOEL for CNS & renal effects in humans (Davis, 1934)
AEGL–2	380 ppm	250 ppm	190 ppm	100 ppm	81 ppm	Nausea, vomiting, headache in humans (Davis, 1934)
AEGL–3	1100 ppm	680 ppm	520 ppm	300 ppm	220 ppm	1-hour rat LC01 (Adams et al., 1952; Dow Chemical, 1986)

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

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

Kowetha Davidson discussed the data set and COT/AEGL's comments (Attachment 7). The COT/AEGL's major concern involved the use of growth retardation from a repeated-exposure developmental toxicity study in rats as the point-of-departure for AEGL-2. Other issues included use of PBPK modeling for interspecies extrapolation and time scaling and justification for the AEGL-3 key study. Jim Dennison stated that PBPK should not be used for the developmental toxicity endpoint, but may be applicable to AEGL-3, depending on the mechanism of death. A discussion on the use of the fetal body weight change focused on the fact that while the 5% change may be biologically significant, it may not represent an AEGL-2 endpoint. George Woodall then presented a benchmark analysis for the rat fetal data (Attachment 8). Bill Snellings indicated that use of the Weller eye data was not appropriate for derivation of AEGL values; he also reminded the committee that his last presentation proposed use of the Sallenfait study (Attachment 9). Because a new approach (fetal benchmark) was presented and the meeting was running out of time, George Rusch postponed discussions on ethylene oxide to the next meeting. Kowetha Davidson, George Woodall, and chemical manager Susan Ripple will work together to resolve issues.

Allyl Alcohol (CAS No. 107-18-6)

Chemical Manager: Nancy Kim, New York
Staff Scientist: Claudia Troxel, CMTox

Claudia Troxel discussed the data set and COT/AEGL's comments (Attachment 10). The COT/AEGL's major concern involved justification of uncertainty factors and rounding of the time scaling exponent 'n' for AEGL-3 values. After discussion, a motion was made by George Woodall and seconded by John Hinz to adopt AEGL-3 values of 36 ppm for 10-minutes, 25 ppm for 30-minutes, 20 ppm for 1 hour, 10 ppm for 4 hours, and 10 ppm for 8 hours. The point-of-departure is a 1-hour NOEL for lethality of 200 ppm in rats, mice, and rabbits (Union Carbide, 1951). Time scaling was accomplished using the default value of n=3 to time scale to the 10- and 30-minute time periods. A MF of 2 was applied to the 1-hour value to obtain the 4- and 8-hour values because only a decrease in body weight was noted in a repeated-exposure study in rats at 20 ppm. The default 'n' value was used because LC_{50} data were not credible for derivation of a chemical-specific exponent. The motion carried (YES: 13; NO: 0; ABSTAIN: 4) (APPENDIX G).

Summary of AEGL Values for Allyl ALcohol						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–3	36 ppm	25 ppm	20 ppm	10 ppm	10 ppm	NOEL lethality in rats, mice, and rabbits (Union Carbide, 1951)

Xylenes (CAS No. 1330-20-7)

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

Claudia Troxel discussed the data set and COT/AEGL's comments (Attachment 11). This xylene TSD is a case study for the PBPK methodology and values proposed followed methodology consistent with the PBPK white paper being sent to the COT. Key issues were whether to apply the UF to the dose-metric or to the human equivalent concentration and whether or not to consider work. Proposed AEGL-1 values were 130 ppm for all time points based on ocular irritation in humans exposed to 400 ppm for 30 minutes (Hastings et al., 1986) with the application of an intraspecies UF of 3. Proposed AEGL-2 values were 2500 ppm for 10-minutes, 1300 ppm for 30-minutes, 920 ppm for 1 hour, 500 ppm for 4 hours, and 500 ppm for 8 hours, and proposed AEGL-3 values were 7200 ppm for 10-minutes, 3600 ppm for 30-minutes, 2500 ppm for 1 hour, 1300 ppm for 4 hours, and 1000 ppm for 8 hours. Proposed AEGL-2 and AEGL-3 values utilized the PBPK modelwith the UF applied to the dose metric. After discussion, a motion was made by Bob Benson and seconded by Bill Bress to adopt AEGL-1, AEGL-2, and AEGL-3 values as proposed. The motion carried (AEGL-1: YES: 13; NO: 0; ABSTAIN: 4) (AEGL-2: YES: 12; NO: 1; ABSTAIN: 4) (AEGL-3: YES: 12; NO: 0; ABSTAIN: 5) (APPENDIX H).

Summary of AEGL Values for Xylenes						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	130 ppm	130 ppm	130 ppm	130 ppm	130 ppm	Eye irritation in humans (Hastings et al., 1986)
AEGL–2	2500 ppm	1300 ppm	920 ppm	500 ppm	400 ppm	PBPK Model
AEGL–3	7200 ppm	3600 ppm	2500 ppm	1300 ppm	1000 ppm	PBPK Model

Bromine (CAS No. 7726-95-6)

Chemical Manager: Ernest Falke, U.S. EPA
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage discussed the data set and COT/AEGL's comments (Attachment 12). The main COT concern was the sparse and conflicting data set. A proposal was made to base the bromine AEGL values on the chlorine AEGL values using a relative toxicity approach. Chlorine has a much more robust database. After discussion, the NAC decided that there was not enough data to merit deriving bromine AEGL values using a relative toxicity approach. A motion was made by Bob Benson and seconded by John Morawetz to revise the AEGL-1 values to be consistent with the SOP. The AEGL-1 was based on eye irritation in humans exposed to 0.1 ppm for 30-minutes; an intraspecies UF of 3 was applied. The AEGL-1 values had previously been scaled across time. The motion was to revise the AEGL-1 values to be constant across all time periods because the endpoint is minor irritation. The resulting value os 0.033 ppm. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (APPENDIX I).

Summary of AEGL Values for Bromine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	0.033 ppm	Eye irritation in humans (Rupp & Henschler, 1967)

Methyl Ethyl Ketone (CAS No. 78-93-3)

Chemical Manager: Bill Bress, Vermont
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage discussed the data set and COT/AEGL's comments (Attachment 13). The COT had suggested using PBPK modeling to derive AEGL values for methyl ethyl ketone. After discussion, the NAC agreed that there is a robust human data set for methyl ethyl ketone and that modeling is not necessary. There were no changes in AEGL values.

REVIEW of PRIORITY CHEMICALS

Hexafluoroacetone (CAS No. 684-16-2)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Bob Young gave a status update for hexafluoroacetone (HFA) (Attachment 14). At NAC/AEGL-36, a suggestion was made to calculate a $BMDL_{05}$ for the AEGL-2 developmental malformation data from the du Pont (1989) rat study. A $BMDL_{05}$ was calculated, and because this is essentially the same as the 1.0 ppm initially used to develop the AEGL-2 values (tentatively approved by a majority vote), no adjustment is needed in the proposed values. The TSD will be revised to reflect the use of the $BMDL_{05}$ assessment in the development of the AEGL-2 values.

SELECTED METAL PHOSPHIDES

ALUMINUM PHOSPHIDE (CAS Reg. No. 20859-73-8)
POTASSIUM PHOSPHIDE (CAS Reg. No. 20770-41-6)
SODIUM PHOSPHIDE (CAS Reg. No. 12058-85-4)
ZINC PHOSPHIDE (CAS Reg. No. 1314-84-7)
CALCIUM PHOSPHIDE (CAS Reg. No. 1305-99-3)
MAGNESIUM PHOSPHIDE (CAS Reg. No. 12057-74-8)
STRONTIUM PHOSPHIDE (CAS Reg. No. 12504-13-1)

MAGNESIUM ALUMINUM PHOSPHIDE (CAS Reg. No. None)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Cheryl Bast reviewed the available data (Attachment15). Appropriate chemical-specific data are not available for derivation of AEGL values for aluminum phosphide, potassium phosphide, sodium phosphide, zinc phosphide, calcium phosphide, magnesium phosphide, strontium phosphide, or magnesium aluminum phosphide.

In the absence of appropriate chemical-specific data for aluminum phosphide, zinc phosphide, calcium phosphide, potassium phosphide, magnesium phosphide, sodium phosphide, strontium phosphide, or magnesium aluminum phosphide, it was proposed that the AEGL-2 and AEGL-3 values for phosphine be used to obtain AEGL-2 and AEGL-3 values, respectively, for the title metal phosphides. The use of phosphine as a surrogate for the metal phosphides is deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from metal phosphides. Because one mole of phosphine is produced for each mole of aluminum phosphide, potassium phosphide, or sodium phosphide hydrolyzed, it was proposed that the phosphine AEGL-2 and AEGL-3 values be adopted as AEGL-2 and AEGL-3 values, respectively, for aluminum phosphide, potassium phosphide, and sodium phosphide. Because a maximum of two moles of phosphine may be produced for each mole of zinc phosphide, calcium phosphide, magnesium phosphide, or strontium phosphide hydrolyzed, it was proposed that the phosphine AEGL-2 and AEGL-3 values be divided by a molar adjustment factor of 2 to derive AEGL-2 and AEGL-3 values, respectively, for zinc phosphide, calcium phosphide, magnesium phosphide, and strontium phosphide. Because a maximum of three moles of phosphine may be produced for each mole of magnesium aluminum phosphide hydrolyzed, it was proposed that the phosphine AEGL-2 and AEGL-3 values be divided by a molar adjustment factor of 3 to derive AEGL-2 and AEGL-3 values, respectively, for magnesium aluminum phosphide. Because AEGL-1 values for phosphine are not recommended (due to insufficient data), AEGL-1 values for the title metal phosphides are also not recommended.

After a short discussion, a motion was made by Richard Niemier and seconded by Susan Ripple to accept the values as proposed. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (APPENDIX J).

AEGL VALUES FOR METAL PHOSPHIDES* (EXPRESSED AS PPM OR MG/M^3 PHOSPHINE)

Compound(s)	Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
Aluminum Phosphide **Potassium Phosphide** **Sodium Phosphide**	**AEGL-1**	NR	NR	NR	NR	NR	Appropriate data not available
	AEGL-2	4.0 ppm (5.6 mg/m^3)	4.0 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.50 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)	Phosphine AEGL-2 values adopted as aluminum phosphide, potassium phosphide, and sodium phosphide AEGL-2 values (NAC/AEGL, 2004).
	AEGL-3	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.90 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)	Phosphine AEGL-3 values adopted as aluminum phosphide, potassium phosphide, and sodium phosphide AEGL-3 values (NAC/AEGL, 2004).
Zinc Phosphide **Calcium Phosphide** **Magnesium Phosphide** **Strontium Phosphide**	**AEGL-1**	NR	NR	NR	NR	NR	Appropriate data not available
	AEGL-2	2.0 ppm (2.8 mg/m^3)	2.0 ppm (2.8 mg/m^3)	1.0 ppm (1.4 mg/m^3)	0.25 ppm (0.36 mg/m^3)	0.13 ppm (0.19 mg/m^3)	Phosphine AEGL-2 values divided by molar adjustment factor of 2 adopted as zinc phosphide, calcium phosphide, magnesium phosphide, and strontium phosphide AEGL-2 values (NAC/AEGL, 2004).
	AEGL-3	3.6 ppm (5.0 mg/m^3)	3.6 ppm (5.0 mg/m^3)	1.8 ppm (2.6 mg/m^3)	0.45 ppm (0.65 mg/m^3)	0.23 ppm (0.32 mg/m^3)	Phosphine AEGL-3 values divided by molar adjustment factor of 2 adopted as zinc phosphide, calcium phosphide, magnesium phosphide, and strontium phosphide AEGL-3 values (NAC/AEGL, 2004).
Magnesium Aluminum Phosphide	**AEGL-1**	NR	NR	NR	NR	NR	Appropriate data not available
	AEGL-2	1.3 ppm (1.9 mg/m^3)	1.3 ppm (1.9 mg/m^3)	0.67 ppm (0.93 mg/m^3)	0.17 ppm (0.24 mg/m^3)	0.08 ppm (0.12 mg/m^3)	Phosphine AEGL-2 values divided by molar adjustment factor of 3 adopted as magnesium aluminum phosphide AEGL-2 values (NAC/AEGL, 2004).
	AEGL-3	2.4 ppm (3.3 mg/m^3)	2.4 ppm (3.3 mg/m^3)	1.2 ppm (1.7 mg/m^3)	0.30 ppm (0.43 mg/m^3)	0.15 ppm (0.21 mg/m^3)	Phosphine AEGL-3 values divided by molar adjustment factor of 3 adopted as magnesium aluminum phosphide AEGL-3 values (NAC/AEGL, 2004).

Staff Scientist: Alexander A. Maslennikov, RIHTOP
Chemical Manager: Ernest Falke, U.S. EPA

Alexander Maslennikov reviewed the data set for dimethylamine (Attachment 16). Vladimir Tchernov served as the translator. AEGL-1 and AEGL-3 values were balloted at NAC-35 (December, 2004) as draft provisional values; therefore, AEGL-2 was emphasized in the presentation. Proposed AEGL-1 values were based on a NOEL for destruction of olfactory epithelium in rats and mice exposed to 10 ppm dimethylamine 6 hours/day, 5 days/week for 6 months (Buckley et al., 1985; CIIT, 1982-83). Uncertainty factors of 3 each for inter- and intraspecies extrapolation were applied. The value was held constant across time. The proposed AEGL-1 value was 10 ppm at all time points. Proposed AEGL-2 values (78 ppm for 10-min, 49 ppm for 30-min, 37 ppm for 1-hour, 21 ppm for 4-hours, and 16 ppm for 8-hours) were based on a NOEL for histopathology in rats exposed to 100 ppm for 6 hours (Gross et al., 1987). An interspecies UF of 3, intraspecies UF of 10, and adjustment factor of 1/3 were proposed. Time scaling was accomplished using an exponent 'n' of 2.4, derived from combined rat and mouse data ranging from 6 to 360 minutes. Proposed AEGL-3 values (560 ppm for 10-min, 350 ppm for 30-min, 260 ppm for 1-hour, 150 ppm for 4-hours, and 110 ppm for 8-hours) were based on a 2 hour rat $BMCL_{05}$ of 1978 ppm (Mezentseva, 1956). Uncertainty factor application and time scaling were proposed as described for AEGL-2.

After discussion, a motion was made by Marc Ruijten and seconded by Richard Niemier to accept AEGL-1 values as proposed. The motion carried (YES: 15; NO: 0; ABSTAIN: 3) (APPENDIX K).

Discussion then focused on AEGL-2 values. The NAC recalculated the value of 'n' for combined rat and mouse data including the Koch data, and obtained a value of n = 2.8. A show-of-hands suggested that there was more support for n = 2.8 for time scaling (rather than the proposed value of 2.6). A motion was then made by Marc Ruijten and seconded by Bob Benson to adopt AEGL-2 values of 130 ppm for 10-min, 85 ppm for 30-min, 66 ppm for 1-hour, 40 ppm for 4-hours, and 32 ppm for 8-hours based on very mild pulmonary irritation in rats exposed to 175 ppm for 6 hours (Gross et al., 1987). Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation and an adjustment factor of ½ was applied because of the minor effect noted at the POD. Time scaling used n = 2.8, and scaling across time was done for all time points because the n value was calculated from lethality data ranging from 6 minutes to 6 hours. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX K).

A motion was then made by Marc Ruijten and seconded by John Hinz to adopt AEGL-3 values of 480 ppm for 10-min, 320 ppm for 30-min, 250 ppm for 1-hour, 150 ppm for 4-hours, and 120 ppm for 8-hours based on the proposed POD (2 hour rat $BMCL_{05}$ of 1978 ppm (Mezentseva, 1956). Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation. Time scaling used n = 2.8. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (APPENDIX K).

Summary of AEGL Values for Dimethylamine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm	NOEL for epithelial damage in in rats and mice in a repeated-exposure study (Buckley et al., 1985; CIIT, 1982-83)
AEGL–2	130 ppm	85 ppm	66 ppm	40 ppm	32 ppm	Mild pulmonary irritation in rats (Gross et al., 1987)
AEGL–3	480 ppm	320 ppm	250 ppm	150 ppm	120 ppm	$BMCL_{05}$ in rats (Mezentseva, 1956)

METHYLAMINE (CAS No. 74-89-5)

Staff Scientist: Lyudmila Tochilkina, RIHTOP
Chemical Manager: Marquea King, U.S. EPA

Marquea King presented the review of methylamine on behalf of Lyudmila Tochilkina (Attachment 17). Proposed AEGL-1 values (15 ppm at all time points) were based on a NOAEL for notable signs of clinical discomfort in rats exposed to 465 ppm for 30 minutes (Jeevaratnam and Srirmachari, 1994). An interspecies UF of 10 and interspecies UF of 3 were proposed. Proposed AEGL-2 values (160 ppm for 10-min, 92 ppm for 30-min, 64 ppm for 1-hour, 31 ppm for 4-hours, and 21 ppm for 8-hours) were based on a NOAEL for lung lesions in rats exposed to 250 ppm methylamine 6 hours/day, 5 days/week for 2 weeks (Kinney et al., 1990). An interspecies UF of 3, intraspecies UF of 10, and adjustment factor of 1/3 were proposed. Time scaling was accomplished using n = 1.9, derived from rat lethality data ranging from 6 to 60 minutes. Proposed AEGL-3 values (1100 ppm for 10-min, 590 ppm for 30-min, 410 ppm for 1-hour, 200 ppm for 4-hours, and 140 ppm for 8-hours) were based on the highest experimental concentration (4100 ppm) causing no lethality in rats exposed to methylamine for 60 minutes (Ulrich et al., 1994). An interspecies UF of 3, intraspecies UF of 10, and adjustment factor of 1/3 were proposed. Time scaling was accomplished using n = 1.9.

After much discussion, a motion was made by Marc Ruijten and seconded by Richard Niemier to adopt AEGL-1 values of 15 ppm for all time points. There will be two key studies, both having equal weight. From the Kinney et al. (1990) study, the POD is 75 ppm for 6 hours. Interspecies UFs of 3 each are applied for inter- and intraspecies extrapolation, which yields a value of 15 ppm. The second key study is as proposed in the draft TSD. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX L). A motion was then made by Bob Benson and seconded by Richard Niemier to accept AEGL-2 values as proposed except that inter- and intraspecies UFs will be 3 each (total = 10). These UFs are considered sufficient and no adjustment factor is needed because the dimethylamine data suggest a similar, but less severe, effect after a single exposure. The motion carried (YES: 15; NO: 1; ABSTAIN: 2) (APPENDIX L). A motion was then made by Richard Niemier and seconded by John Hinz to adopt AEGL-3 values as proposed except that UFs of 3 each

will be applied for inter- and intraspecies extrapolation. The motion carried (YES: 17; NO: 0; ABSTAIN: 0) (APPENDIX L).

Summary of AEGL Values for Methylamine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	15 ppm	15 ppm	15 ppm	15 ppm	15 ppm	NOEL for clinical signs in rats (Kinney et al., 1990; Jeevaratnam and Sriramachari, 1994)
AEGL–2	160 ppm	92 ppm	64 ppm	31 ppm	21 ppm	NOEL for lung lesions in rats- repeated exposure (Kinney et al., 1990)
AEGL–3	910 ppm	510 ppm	350 ppm	170 ppm	110 ppm	NOEL for lethality in rats (Ulrich et al., 1994)

TRIMETHYLAMINE (CAS No. 75-50-3)

Staff Scientist: Valentin Ye. Zhukov, RIHTOP
Chemical Manager: Iris Camacho, U.S. EPA

Iris Camacho presented the review of trimethylamine on behalf of Valentin Ye. Zhukov (Attachment 18). No AEGL-1 values were proposed because of insufficient data. Proposed AEGL-2 values (100 ppm for 10-min, 68 ppm for 30-min, 51 ppm for 1-hour, 29 ppm for 4-hours, and 22 ppm for 8-hours) were based on a NOAEL for tracheal effects in rats exposed to 250 ppm trimethylamine, 6 hours/day, 5 days/week for 2 weeks (Kinney et al., 1990). An interspecies UF of 3 was proposed because lethality data from rats and mice suggest little interspecies variability. An intraspecies UF of 10 was proposed due to metabolic polymorphism in humans, and an adjustment factor of 1/3 was proposed to obtain AEGL-2 values consistent with the total database. Time scaling was accomplished using n= 2.5, derived from rat lethality data ranging from 20-min to 4-hours. Proposed AEGL-3 values (750 ppm for 10-min, 490 ppm for 30-min, 380 ppm for 1-hour, 220 ppm for 4-hours, and 170 ppm for 8-hours) were based on 20-minute and 1-hr $BMCL_{05}$ values in rats (IRDC, 1992). An interspecies UF of 3 was proposed because lethality data from rats and mice suggest little interspecies variability. An intraspecies UF of 10 was proposed due to metabolic polymorphism in humans, and an adjustment factor of 1/3 was proposed to obtain AEGL-2 values consistent with the total database. Time scaling was accomplished using n= 2.5, derived from rat lethality data ranging from 20 min to 4 hours.

After discussion, a motion was made by Tom Hornshaw and seconded by Ernest Falke to adopt AEGL-1 values of 8 ppm for all time points. This is based on human occupational monitoring data (AIHA, 1980) indicating no toxic effects in workers exposed to 0.1-8 ppm trimethylamine. This value also is supported by the relative toxicity to dimethylamine. The motion carried (YES: 12; NO: 1; ABSTAIN: 5) (APPENDIX M). A motion was then made by Marc Ruijten and seconded by Ernest Falke to adopt AEGL-2 values of (240 ppm for 10-min, 150 ppm for 30-min, 120 ppm for 1-hour, 67 ppm for 4-hours, and 51 ppm for 8-hours). The point-of-departure is an estimated threshold

for AEGL-2 effects (Kinney, 1990); no rats died when exposed to 2000 ppm for 4 hours; however, 3/6 rats died at 3500 ppm. The 2000 ppm concentration was divided by 3 to obtain the POD. Inter- and intraspecies UFs of 3 each were applied, and time scaling was performed as proposed in the TSD. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX M). Finally, a motion was made by Bob Benson and seconded by Steve Barbee to accept the AEGL-3 values as proposed except to apply inter- and intraspecies UFs of 3 each and eliminate the adjustment factor. The motion carried (YES: 12; NO: 1; ABSTAIN: 5) (APPENDIX M).

Summary of AEGL Values for Trimethylamine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	8.0 ppm	8.0 ppm	8.0 ppm	8.0 ppm	8.0 ppm	NOEL for effects in workers (AIHA, 1980)
AEGL–2	240 ppm	150 ppm	120 ppm	67 ppm	51 ppm	Estimated threshold for AEGL-2 effects (Kinney et al., 1990)
AEGL–3	750 ppm	490 ppm	380 ppm	220 ppm	170 ppm	20-min and 1-hr $BMCL_{05}$ in rats (IRDC, 1992)

ETHYLAMINE (CAS No. 75-04-7)

Staff Scientist: Valery Kiryukhin, RIHTOP
Chemical Manager: Marquea King, U.S. EPA

Marquea King presented the review of ethylamine on behalf of Valery Kiryukhin (Attachment 19). No AEGL-1 values were proposed because of insufficient data. Proposed AEGL-2 values (260 ppm for 10-min, 180 ppm for 30-min, 57 ppm for 1-hour, 25 ppm for 4-hours, and 16 ppm for 8-hours) were one-third the proposed AEGL-3 values. Proposed AEGL-3 values (770 ppm for 10-min, 530 ppm for 30-min, 170 ppm for 1-hour, 74 ppm for 4-hours, and 49 ppm for 8-hours) were based on 6-min, 20-min and 60-min $BMCL_{05}$ values in rats (IRDC, 1993). An interspecies UF of 3, intraspecies UF of 10, and adjustment factor of 1/3 were proposed. Time scaling was accomplished using n = 1.7, derived from rat lethality data ranging from 6-minutes to 1-hour).

A motion was made by Bob Benson and seconded by Tom Hornshaw to accept the AEGL-3 values as proposed, except to use n = 1.6 (810 ppm for 10-min, 420 ppm for 30-min, 270 ppm for 1-hour, 120 ppm for 4-hours, and 76 ppm for 8-hours), calculated by Marc Ruijten at the meeting (rather than n= 1.7, proposed in the TSD). The motion carried (YES: 18; NO: 0; ABSTAIN: 1) (APPENDIX N). {The AEGL-1 and AEGL-2 discussions were deferred until the three other amine chemicals were discussed.]

A motion was then made by Marc Ruijten and seconded by Bob Benson to adopt AEGL-2 values of (150 ppm for 10-min, 76 ppm for 30-min, 49 ppm for 1-hour, 22 ppm for 4-hours, and 14 ppm for 8-hours) based on one-third the AEGL-3 values. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX N). A motion was then made by Tom Hornshaw and seconded by Richard Niemier to adopt AEGL-1 values for ethylamine by dividing the methylamine AEGL-1 values by 2 (applying a

MF of 2). Support for this approach is that the RD_{50} values are similar for methylamine and ethylamine and that there are no appropriate data for ethylamine (MF support). This yields an AEGL-1 of 7.5 ppm for all time points. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (APPENDIX N).

Summary of AEGL Values for Ethylamine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	7.5 ppm	7.5 ppm	7.5 ppm	7.5 ppm	7.5 ppm	Methylamine AEGL-1 values ÷2
AEGL–2	150 ppm	76 ppm	49 ppm	22 ppm	14 ppm	1/3 AEGL-3 values
AEGL–3	810 ppm	420 ppm	270 ppm	120 ppm	76 ppm	6-min, 20-min and 1-hr $BMCL_{05}$ in rats (IRDC, 1993)

LEVEL OF ODOR AWARENESS (LOA)

DIMETHYLAMINE(CAS No. 124-40-3)
METHYLAMINE(CAS No. 74-89-5)
TRIMETHYLAMINE(CAS No. 75-50-3)
ETHYLAMINE (CAS No. 75-04-7)

After the discussions of the four amine chemicals were complete, a motion was made by Marc Ruijten and seconded by Bob Benson to adopt LOA values of 0.53 ppm for dimethylamine, 0.56 ppm for methylamine, 0.00051 ppm for trimethylamine, and 0.74 ppm for ethylamine. The motion carried unanimously be a show of hands (Appendix O).

Bis-Chloromethyl Ether (BCME) (CAS No. 542-88-1)

Staff Scientist: Sylvia Milanez
Chemical Manager: Ernest Falke, U.S. EPA

Sylvia Milanez discussed the available data (Attachment 20). AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation. Proposed AEGL-2 values (0.055 ppm for 10-min, 0.055 ppm for 30-min, 0.044 ppm for 1-hour, 0.028 ppm for 4-hours, and 0.020 ppm for 8-hours) were based on an estimated NOAEL for irreversible respiratory lesions in rats and hamsters (Drew et al., 1975). Animals exposed to 0.7 ppm for 7 hours and observed for a lifetime, showed increased lung to body weight ratio. This 0.7 ppm concentration was divided by 3 to obtain the POD of 0.23 ppm. An interspecies UF of 3 was applied and is considered sufficient because BCME caused a similar response in two species. An intraspecies UF of 3 was also applied because BCME is a proximally-acting irritant with a steep concentration-response curve. Time scaling was performed with the default values of n = 1 or n = 3. Proposed AEGL-3 values (0.23 ppm for 10-min, 0.23 ppm for 30-

min, 0.18 ppm for 1-hour, 0.11 ppm for 4-hours, and 0.075 ppm for 8-hours) were based on a NOEL for lethality from lung lesions in rats and hamsters exposed to 1 ppm for 6 hours (Drew et al., 1975). Uncertainty factor application and time scaling were proposed similar to AEGL-2.

After discussion, a motion was made by Marc Ruijten and seconded by Bob Benson to adopt all values as proposed with a notation on every table containing AEGL-2 values stating that cancer risk is greater than AEGL-2 values. Also, cancer risk will be calculated at the AEGL-2 and AEGL-3 cvalue concentrations and will be included in the TSD. The motion carried (YES: 15; NO: 3; ABSTAIN: 0) (APPENDIX P).

Summary of AEGL Values for BCME						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended
AEGL–2	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm	Estimated NOAEL for irreversible respiratory lesions in rats and hamsters (Drew et al., 1975)
AEGL–3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm	NOEL for lethality from lung lesions in rats and hamsters (Drew et al., 1975).

Chloromethyl Methyl Ether (CMME) (CAS No. 107-30-2)

Staff Scientist: Sylvia Milanez
Chemical Manager: Ernest Falke, U.S. EPA

Sylvia Milanez discussed the available data (Attachment 21). (This TSD is interim status and has previously been to the COT subcommittee; however, the summary is presented here because of the relationship of CMME and BCME). AEGL-1 values were not recommended because no studies were available in which toxicity was limited to AEGL-1 effects. Proposed AEGL-2 values (0.34 ppm for 10-min, 0.34 ppm for 30-min, 0.27 ppm for 1-hour, 0.17 ppm for 4-hours, and 0.12 ppm for 8-hours) were based on an estimated NOAEL for irreversible respiratory lesions in rats and hamsters (Drew et al., 1975). Animals exposed to 12.5 ppm for 7 hours and observed for 14-days, showed increased lung congestion, edema, and hemorrhage. This 12.5 ppm concentration was divided by 3 to obtain the POD of 4.3 ppm. An interspecies UF of 3 was applied and is considered sufficient because CMME caused a similar response in two species. An intraspecies UF of 3 was also applied because CMME is a proximally-acting irritant. A modifying factor of 3 was applied because the content of BCME (which is more toxic than CMME) in technical grade CMME in the key study is unknown, and 3 is the geometric mean of the typical range of 1-10% BCME concentration. Time scaling was performed with the default values of n = 1 or n = 3. Proposed AEGL-3 values (1.4 ppm for 10-min, 1.4 ppm for 30-min, 1.1 ppm for 1-hour, 0.72 ppm for 4-hours, and 0.53 ppm for 8-

hours) were based on a 7 hour $BMCL_{05}$ of 18 ppm in hamsters (Drew et al., 1975). Uncertainty factor and modifying factor application and time scaling were proposed similarly to AEGL-2.

After discussion, a motion was made by Richard Niemier and seconded by John Hinz to adopt AEGL values as proposed except to apply a modifying factor of 1.7, rather than 3. This MF of 1.7 is based on relative potency calculations as follows: MF = (0.1 x 55/7) + (0.9 x 1) = 1.7. The motion carried (YES: 16; NO: 1; ABSTAIN: 0) (Appendix Q).

Summary of AEGL Values for CMME						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended
AEGL–2	0.60 ppm	0.60 ppm	0.47 ppm	0.30 ppm	0.22 ppm	Estimated NOAEL for irreversible respiratory lesions in rats and hamsters (Drew et al., 1975)
AEGL–3	2.6 ppm	2.6 ppm	2.0 ppm	1.3 ppm	0.93 ppm	7-hr $BMCL_{05}$ in hamsters (Drew et al., 1975).

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-38: September 28-30, 2005, Washington DC
NAC/AEGL-39: December 13-15, 2005, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Bob Young, Oak Ridge National Laboratory, 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-37 Meeting Agenda
Attachment 2. NAC/AEGL-38 Attendee List
Attachment 3. Uncertainty Factor Analysis
Attachment 4. Response to COT comments for sulfur dioxide
Attachment 5. Response to COT comments for chloroform
Attachment 6. Response to COT comments for carbon tetrachloride
Attachment 7. Response to COT comments for ethylene oxide
Attachment 8. Benchmark analysis for ethylene oxide fetal rat data
Attachment 9. Bill Snelling's ethylene oxide presentation
Attachment 10. Response to COT comments for allyl alcohol
Attachment 11. Response to COT comments for xylenes
Attachment 12. Response to COT comments for bromine
Attachment 13. Response to COT comments for methyl ethyl ketone
Attachment 14. Status update- hexafluoroacetone
Attachment 15. Data analysis for metal phosphides
Attachment 16. Data analysis for dimethylamine
Attachment 17. Data analysis for methylamine
Attachment 18. Data analysis for trimethylamine
Attachment 19. Data analysis for ethylamine
Attachment 20. Data analysis for BCME
Attachment 21. Data analysis for CMME

LIST OF APPENDICES

Appendix A. Ballot for final meeting highlights of NAC/AEGL-36
Appendix B. Final meeting highlights of NAC/AEGL-36
Appendix C. Ballot for PBPK white paper
Appendix D. Ballot for sulfur dioxide
Appendix E. Ballot for chloroform
Appendix F. Ballot for carbon tetrachloride
Appendix G. Ballot for allyl alcohol
Appendix H. Ballot for xylenes
Appendix I. Ballot for bromine
Appendix J. Ballot for selected metal phosphides
Appendix K. Ballot for dimethylamine
Appendix L. Ballot for methylamine
Appendix M. Ballot for trimethylamine
Appendix N. Ballot for ethylamine
Appendix O. Ballot for amine LOA values
Appendix P. Ballot for BCME
Appendix Q. Ballot for CMME
Appendix R. AEGL Committee Chairman Certification of Minutes

National Advisory Committee for
Acute Exposure Guideline Levels for Hazardous Substances

ATTACHMENT 1

NAC/AEGL-37
June 13-15, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., N.W.
Washington, DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Monday, June 13, 2005

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-36 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
	Progress report (Ernie Falke) and Uncertainty Factor Review (Iris Camacho)
10:30	Revisit of Dimethylamine (Ernie Falke/Alexander Maslennikov)
11:30	Revisit of Hexafluoroacetone: AEGL-2 (Paul Tobin/Bob Young)
12:00 p.m.	Revisit of Sulfur Dioxide- COT Comments (George Woodall/Cheryl Bast)
12:30	Lunch
1:30	Revisit of Bromine- Status Update (Ernie Falke/Sylvia Talmage)
2:00	Revisit of Chloroform- COT Comments (Steve Barbee/Bob Young)
3:00	Break
3:15	Review of Ethyl Amine (Marquea King/Valery Kiryukhin)
4:30	Review of Selected Metal Phosphides (George Cushmac/Cheryl Bast)
5:30	Adjourn for the day

Tuesday, June 14, 2005

8:30 a.m.	Review of Methyl amine (Marquea King/Lyudmila Tochilkina)
10:00	Break
10:15	Review of Trimethylamine (Iris Camacho/Valentin Zhukov)
12:00 p.m.	Lunch
1:00	Review of BCME and CMME (Ernie Falke/Sylvia Milanez)
3:00	Break
3:15	Revisit of Carbon Tetrachloride- COT comments (Bill Bress/Bob Young)
4:15	Revisit of Ethylene Oxide- COT Comments (Susan Ripple/Kowetha Davidson)
5:30	Adjourn for the day

Wednesday, June 15, 2005

8:00 a.m.	PBPK White Paper Discussion/ COT Comments Xylenes (Bob Benson/Jim Dennison/Claudia Troxel)
10:00	Break
10:15	Revisit of Methyl Ethyl Ketone-Status Update (Bill Bress/Sylvia Talmage)
10:30	Revisit of Allyl Alcohol- COT Comments and New Data (Nancy Kim/Claudia Troxel)
11:30	Administrative matters
12:00 noon	Adjourn meeting

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

19/23 present

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz	A			
Jonathan Borak	A				Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers	A			
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas	A			
Tom Hornshaw					George Woodall				
Warren Jederberg	A								
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

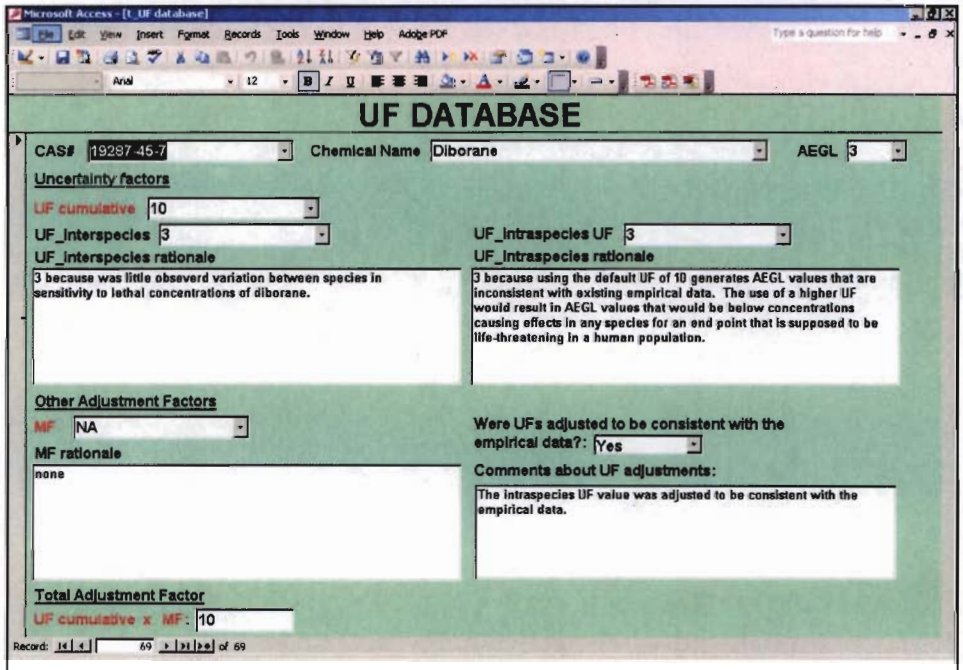
AEGL 1 Motion by: _____ **Second by:** _____
AEGL 2 Motion by: _____ **Second by:** _____
AEGL 3 Motion by: _____ **Second by:** _____
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** _____

Uncertainty Factor (UF) Review

- As of April 2005, the AEGL Program has developed 64 interim and 24 final chemicals (total=88)
- NAC members have reviewed the UF rationales for 63 chemicals (72%)
- Access database was created to collect information about UF usage
  - 23 chemicals currently in database

NAC-37/ June 13,2005



NAC-37/ June 13,2005

ATTACHMENT 4

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFUR DIOXIDE

Response to COT Comments

NAC/AEGL-37
June 13-15, 2005

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Woodall

Comments on sulphur dioxide interim 1

14 March 2005

The NAS Subcommittee on AEGLs agreed that this is a well-written document and had only relatively minor suggestions for improvement.

Derivation of AEGL-1

The comment on page 27, line 32 that .25 may be a threshold contradicts the comment on page 28 line 3 that effects were found at .25 ppm. In any case, it must be realised that effective concentrations in asthmatics are highly dependent upon the 'severity' of the disease in the subjects being tested, the extent of medication use, etc. Thus, one study may show an effect at a concentration showing no effect in another study merely due to differences in subjects. Asthmatics are a highly variable group in terms of response to exposure to irritants, much more so than normal individuals exposed to the same atmospheres. Furthermore, most controlled clinical studies generally use subjects who are not the most severe. Based upon all this, I feel that the value for AEGL-1 of 0.25 ppm is too high and should be reduced to account for susceptibility differences in the most sensitive population, namely asthmatics. I would suggest a value of 0.2 ppm at the highest. I do agree that the time should be held constant across the board.

Derivation of AEGL-2

The argument above for AEGL-1 applies here as well. Changes in airway resistance of almost 600% is not necessarily of little consequence to an asthmatic.

Conclusions of the Subcommittee re sulphur dioxide:

The AEGL-1 should be set at 0.2 ppm across the time scale.
The AEGL-2 should be 0.75 throughout.
The AEGL-3 remains as proposed.

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
~~0.25 ppm~~ *0.20 ppm*	~~0.25 ppm~~ *0.20 ppm*	~~0.25 ppm~~ *0.20 ppm*	~~0.25 ppm~~ *0.20 ppm*	~~0.25 ppm~~ *0.20 ppm*
~~Weight-of-evidence approach suggests 0.25 ppm is threshold for mild bronchoconstriction in exercising asthmatics~~ *Weight-of-evidence approach suggests 0.20 ppm is NOEL for bronchoconstriction in exercising asthmatics*				
Time Scaling: Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-1 values for SO_2 will be held constant across all time points.				
Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.				

WEIGHT OF EVIDENCE FOR AEGL-1

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.2 ppm	5 min	8	23 °C, 85% RH, exercise 48 L/min	none	Linn et al., 1983b
0.25 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	none	Schacter et al., 1984
0.25 ppm	5 min	199	23 °C, 36% RH, exercise 60 L/min 23 °C, 36% RH, exercise 80-90 L/min	SRaw ↑134% SRaw ↑139%	Bethel et al., 1985
0.25 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min intermittent	none	Roger et al., 1985
0.4 ppm	5 min	23	23 °C, 85% RH, exercise 48 L/min	SRaw ↑69% $V_{max25-75}$ ↓10%	Linn et al., 1983b
0.5 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	none	Schacter et al., 1984

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
~~1.0 ppm~~ *0.75 ppm*	~~1.0 ppm~~ *0.75 ppm*	~~1.0 ppm~~ *0.75 ppm*	0.75 ppm	0.75 ppm
Weight-of-evidence approach suggests 1.0 ppm induces moderate to severe, but reversible, respiratory response in exercising asthmatics, based on the fact that asthmatics developed increased airway resistance of 102% to 580% for exposure durations of 5- to 75-min. The same response was seen at 0.75 ppm for exposure durations of 10-min to 3-hr.				
Time Scaling: The role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure. Data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure. Therefore, AEGL-2 values for SO_2 were held constant across *all* time points. ~~for the 10-min, 30-min, and 1-hr values. Because the maximum duration for a 1.0 ppm exposure of asthmatics was 75-minutes, and data were available at 0.75 ppm for up to 3 hours, the 4- and 8-hour AEGL-2 values were held constant at 0.75 ppm.~~				
Data adequacy: Robust data base of controlled studies in both healthy and asthmatic humans.				

WEIGHT OF EVIDENCE FOR AEGL-2

Concentration	Duration	Subjects	Exposure Parameters	Effect	Reference
0.75 ppm	3 hours	17	22 °C, 85% RH, exercise 45 L/min (first 10-min of exposure)	SRaw ↑: 322% (at 10-min) 233% (at 20-min) 26% (at 1-hr) 5% (at 2-hr) FEV_1 :↓20% (at 15-min)	Hackney et al., 1984
0.75 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑150% FEF ↓22% FEV_1 ↓8%	Schacter et al., 1984
1.0 ppm	10-40 min	10	23 °C, 70% RH, exercise 35 L/min	SRaw ↑470% FEF ↓27% FEV_1 ↓14%	Schacter et al., 1984
1.0 ppm	75 min	28	26 °C, 70% RH, exercise 42 L/min, intermittent	SRaw ↑300%	Roger et al., 1985
1.0 ppm	30 min	10	26 °C, 70% RH, exercise 41 L/min (3- 10 min periods separated by rests of 15 min)	SRaw ↑172% SRaw ↑137% SRaw 106%	Kehrl et al., 1987
1.0 ppm	30 min	10	26 °C, 70% RH, continuous exercise 41 L/min	SRaw ↑233%	Kehrl et al., 1987
1.0 ppm	1 min 3 min 5 min	8	22 °C, 75% RH, exercise 60 L/min	SRaw ↑93% SRaw ↑395% SRaw ↑580%	Balmes et al., 1987
1.0 ppm	0.5 min 1.0 min 2.0 min 5.0 min	12	20 °C, 40% RH, exercise 40 L/min	No SRaw effect No SRaw effect SRaw ↑121% SRaw ↑307%	Horstman et al., 1988

CHLOROFORM AEGL

NRC/COT Subcommittee Issues

NAC/AEGL 37
June 13-15, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., NW
Washington DC 20210

CHLOROFORM

- **AEGL-1**

  Concurred with 'Not Recommended'

- **AEGL-2**

  Concurred with values

CHLOROFORM

- **AEGL-3**
  - **Major issue: AEGL-3 values are overly conservative**
  - **Suggestion: need to raise AEGL-3 values**
    - **use anesthesia data from Whitaker and Jones (1965) and no intraspecies UF but apply an MF**
    - **use PBPK model results**

CHLOROFORM

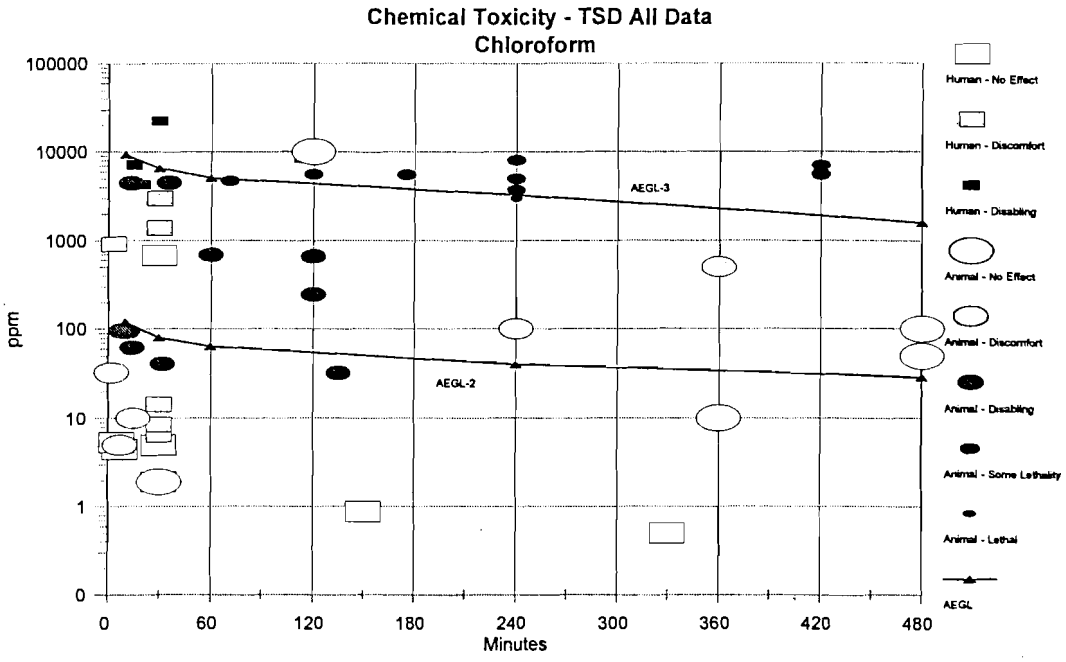
PROPOSED RESPONSE

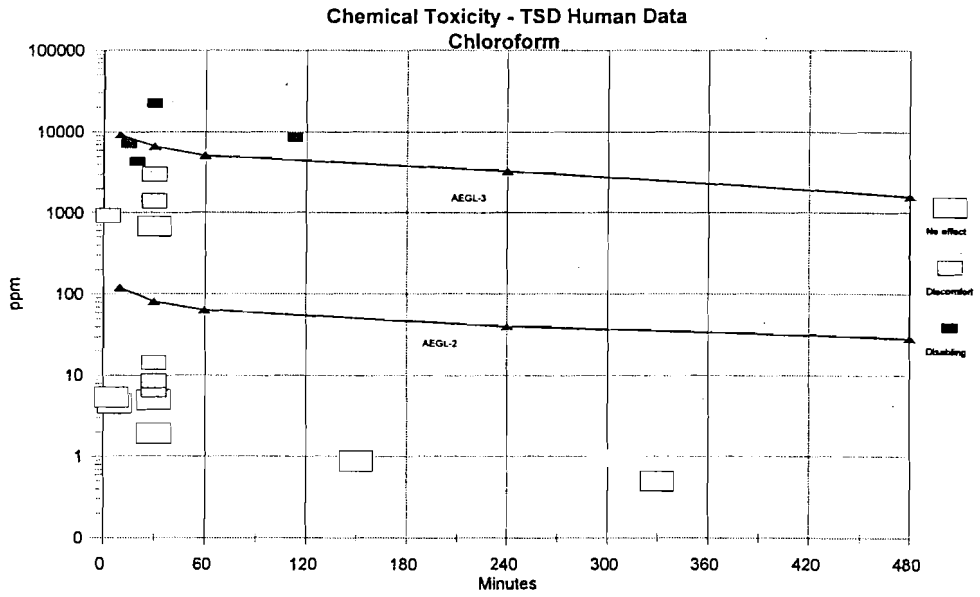
- anesthesia data lack exposure duration-concentration relationship

- PBPK model (Delic et al., 2000) shows rate of metabolism of $CHCl_3$ in mice is 25-50X greater than humans
  - metabolism is a factor for lethal response at 24 hrs post exposure (Lundberg et al., 1986)
  - interspecies UF likely <<1
  - no data to justify additional reduction of intraspecies UF of 3

- adjust AEGL-3 values with WOEF of 1/3 to account for mouse>rat>human metabolism/dosimetry differential
  - differential is 25-50 fold between mouse and human
  - differential between rat and human ???
    - assume midway between 25-50 fold difference of mice and humans (i.e., ~35 fold); WOEF of 1/3 appears justified

PROPOSED AEGL VALUES FOR CHLOROFORM						
AEGL Level	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Not recommended; AEGL-1 effects unlikely to occur in the absence of notable toxicity.
AEGL-2	120 ppm	80 ppm	64 ppm	40 ppm	29 ppm	Fetotoxicity/embryo-lethality in rats exposed for 7 hrs/day on gestation days 6-15 (Schwetz et al., 1974); single exposure assumed
AEGL-3	~~3100 ppm~~ 9,300 ppm	~~2200 ppm~~ 6,600 ppm	~~1700 ppm~~ 5,100 ppm	~~1100 ppm~~ 3,300 ppm	~~540 ppm~~ 1,600 ppm	Estimated lethality threshold for rats; 3-fold reduction in 4-hr LC_{50} of 9780 ppm to 3260 ppm (Lundberg et al., 1986)


Chemical Toxicity - TSD All Data
Chloroform
ppm
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL


Chemical Toxicity - TSD Human Data
Chloroform
ppm
Minutes
AEGL-3
AEGL-2
No effect
Discomfort
Disabling

CARBON TETRACHLORIDE AEGL

NRC/COT Subcommittee Issues

NAC/AEGL 37
June 13-15, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., NW
Washington DC 20210

CARBON TETRACHLORIDE

- **NRC/COT Subcommittee considered uncertainty factors to be excessive; current AEGLs are too low**
  - **suggested using PBPK models to support a reduction in the intraspecies UF.**
  - **suggested that the information from the PBPK models might be used to reassess the time scaling to avoid overly conservative values especially when extrapolating to longer time points**
  - **alternative approaches (varying POD, UFs, etc.) were suggested**

CARBON TETRACHLORIDE

- **AEGL-1**

  - **suggest intraspecies UF of 3 rather than 10**
    - **little individual variability (including variability between elderly and infants) is observed in the CNS response to VOC anesthetics (de Jong et al., 1975; Gregory et al., 1969; Stevens et al., 1975)**
    - **variability in hepatic and renal toxicity (CYP2E1-mediated) likely irrelevant at AEGL-1 exposures**
    - **heavy drinker noted in Norwood et al. (1950) was likely exposed to much greater concentrations than 250 ppm**
    - **exposures of 100 ppm for 2-2.5 hrs required for alcohol-potentiation of CCl_4-induced hepatotoxicity in rats (Cornish et al., 1967)**

  - **Time scaling using $C^n \times t = k$ is questionable; excessively low AEGL values with increasing time**
    - **use a NOAEL for CNS and renal effects (Davis, 1934) of 76 ppm for 4 hrs as POD; requires less extrapolation (4 hrs to 8 hrs rather than 30 min to 8 hrs)**
    - **VOC-induced CNS effects are generally attributed to parent compound at the CNS site (neuronal membrane), therefore only modest increases in neuronal dysfunction will occur once near-steady state is attained (Moser and Balster, 1985; Bruckner et al., 2004).**
    - **as time increases, exposure concentration values should not be as low as those determined by a $C^n \times t = k$ approach.**

CARBON TETRACHLORIDE

- **AEGL-2**

  - **Uncertainty factor application is excessive: suggest intraspecies UF of 3 rather than 10**

    - **UF of 10 to account for metabolism-mediated effects is irrelevant for a CNS effect**

    - **suggested using a LOAEL of 317 ppm for 30 min. for nausea/vomiting/headache (Davis, 1934) as POD**

    - **additional human exposure data suggest that AEGL-2 values are too low:**

      - **49 ppm for 70 min was without ill effect (Stewart et al., 1961)**

      - **11 ppm for 3 hrs resulted in no effect (Stewart et al., 1961)**

      - **no CNS depression or renal toxicity in humans exposed to 76 ppm for 4 hrs (Davis (1934)**

CARBON TETRACHLORIDE

- **AEGL-3**

  - **PBPK models indicate that rodents achieve higher doses to target organs/tissues due to relatively more rapid respiration, heart rate and blood flow rates, and higher blood:air partition coefficients (Gargas et al., 1989).**

  - **A CCl_4 PBPK model has shown that rats exhibit greater metabolism of CCl_4 and are more susceptible than humans to CCl_4 metabolite-induced cytotoxicity (Delic et al., 2000). This is adequate justification for retaining an interspecies UF of 3.**

CARBON TETRACHLORIDE

ISSUE

- **NRC/COT Subcommittee indicated that AEGL-3 value were overly conservative.**

- **While the PBPK models suggest that the interspecies UF should remain at 3, the models do not justify reduction of the intraspecies UF (10 ⇒ 3) used for AEGL-3 development because metabolism processes may be a factor in lethality.**

- **If AEGL-2 values are increased due to reduction of the UF and no adjustment made to the AEGL-3 values, AEGL-2 values will be similar to those for AEGL-3.**

CARBON TETRACHLORIDE

ISSUE- RESPONSE PROPOSAL

- **Apply WOEF (Weight-of-Evidence-Factor) of 1/3 to increase the AEGL-3 values without reducing the intraspecies UF of 10.**

  - **CCl_4-induced lethality may be due, in part, to pulmonary damage, CNS effects, as well as renal damage for longer AEGL-specific time periods.**

  - **PBPK model work by Delic et al. (2000), which compared the slowest metabolism in rats to the most rapid metabolism in humans, showed a ratio of 2.7.**

  - **WOEF invoked to adjust for overly conservative AEGL-3 values:**

    - **AEGL-3 consistent with SOPs appeared overly conservative relative to the results from studies (especially multiple exposure studies) in rats (a clearly more sensitive species) that showed no lethality at exposures notably higher than the originally proposed AEGL-3 values.**

    - **Resulting WOEF-adjusted AEGL-3 values remain lower than exposures causing lethality (see category plots).**

CARBON TETRACHLORIDE

- **Data from multiple exposure studies (Union Carbide Corp., 1947; David et al., 1981; Smyth et al., 1936) in rats (the more sensitive species) reveal only minor effects and no lethality above AEGL-3 values.**

  - **exposure of rhesus monkeys to 200 ppm, 8 hrs/day, 5 days/week for 10.5 months resulted in only transient hepatic injury (Smyth et al., 1936)**

  - **exposure of rats to 1500 ppm (varying exposure regimens all of which had Ct of 4500 ppm-hrs) caused hepatic injury (Van Stee et al., 1982)**

  - **exposure of rats to 200 ppm, 8 hrs/day, 5 days/week for 10.5 months had no significant effects (Smyth et al. 1936, and exposure of dogs (400 ppm, 7 hrs/day for 6 months) resulted in decreased body weight.**

CARBON TETRACHLORIDE

Adjusting AEGL values as per COT suggestions: AEGL-1 developed using a POD NOAEL (CNS and renal effects) of 76 ppm for 4 hrs and an intraspecies UF of 3, AEGL-2 developed using an intraspecies UF of 3, and AEGL-3 adjusted with a WOEF of 1/3 results in the following AEGL values:

AEGL VALUES FOR CARBON TETRACHLORIDE (ppm)						
Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	~~25~~ 58	~~16~~ 58	~~12~~ 44	~~6.9~~ 25	~~5.2~~ 19	~~Nervousness and slight nausea in human subjects exposed for 30 minutes to 158 ppm~~; No CNS or renal effects in humans subjects exposed to 76 ppm for 4 hrs; UF=3 (Davis, 1934)
AEGL-2	~~114~~ 380	~~74~~ 250	~~56~~ 190	~~32~~ 100	~~24~~ 81	Nausea, vomiting, headache in human subjects exposed to 1191 ppm for 9 minutes; ~~UF=10~~ UF=3 (Davis, 1934)
AEGL-3[a]	~~350~~ 1000	~~230~~ 690	~~170~~ 500	~~99~~ 300	~~75~~ 230	Lethality in rats; estimated LC_{01}; UF= 3 x 10 (Adams et al., 1952; Dow Chemical, 1986); WOEF 1/3

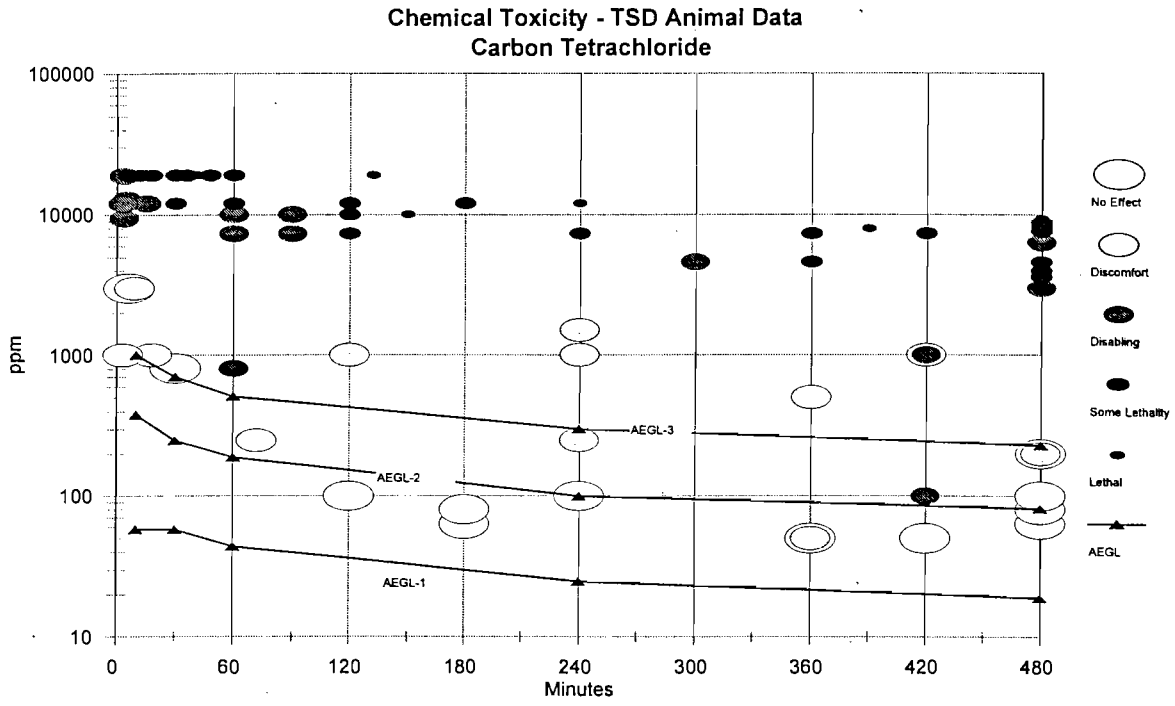
[a] The original POD for AEGL-3 was an estimated 1-hr LC_{01} of 5153.5 ppm derived from a Litchfield Wilcoxon analysis of rat lethality data. A BMD analysis of these data resulted in a $BMDL_{05}$ of 6241.47 ppm.

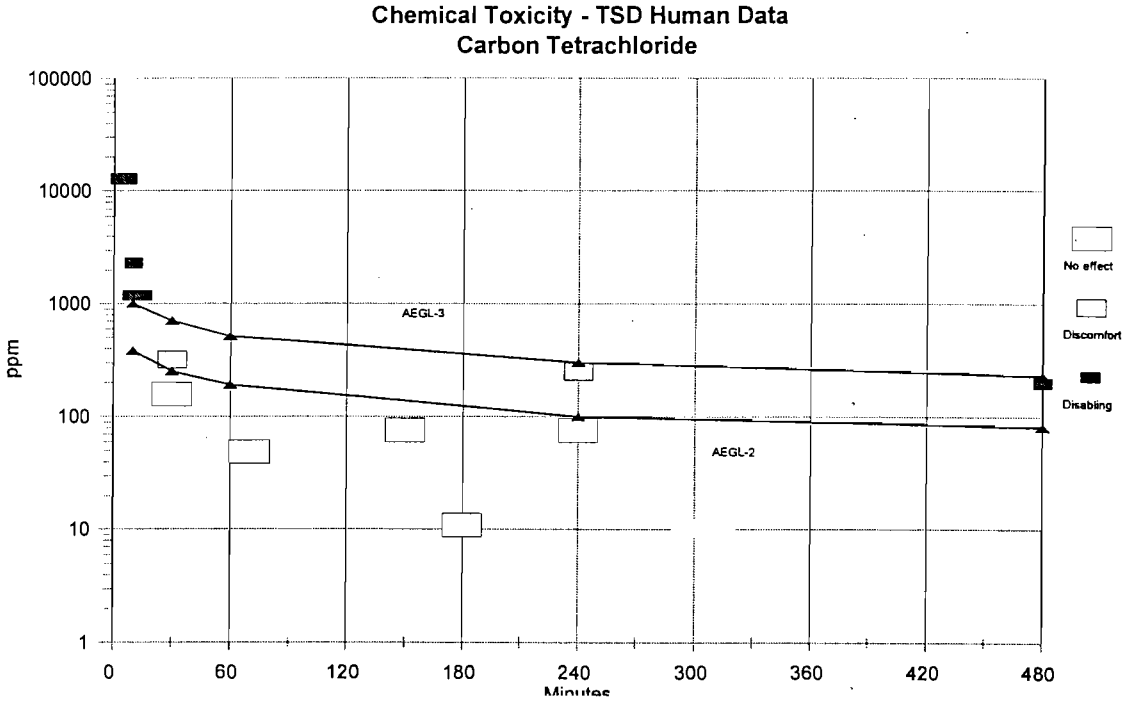
CARBON TETRACHLORIDE

A BMD analysis of these data resulted in a $BMDL_{05}$ of 6241.47 ppm. The AEGL-3 values based upon the $BMDL_{05}$ (UF = 3 x 10) are shown below

	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-3	430 ppm 1300 ppm	280 ppm 840 ppm	210 ppm 630 ppm	120 ppm 360 ppm	90 ppm 270 ppm	Lethality in rats; $BMDL_{05}$; UF= 3 x 10 (Adams et al., 1952; Dow Chemical, 1986)

WOEF-adjusted (1/3) values are on the 2nd line


Chemical Toxicity - TSD Animal Data
Carbon Tetrachloride
100000
10000
1000
100
10
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
No Effect
Discomfort
Disabling
Some Lethality
Lethal
AEGL


Chemical Toxicity - TSD Human Data
Carbon Tetrachloride
100000
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
AEGL-3
AEGL-2
No effect
Discomfort
Disabling

#15

RESPONSE TO COT COMMENTS ON THE ETHYLENE OXIDE (ETO) TSD

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SUSAN RIPPLE, CHEMICAL MANAGER

NAC/AEGL MEETING, WASHINGTON, DC
JUNE 13-15, 2005

ATTACHMENT 7

RESPONSE TO COT ISSUES

- PRIMARY ISSUE IS THE DERIVATION OF AEGL-2:
  - Using growth retardation as the endpoint in a repeat exposure developmental toxicity study
  - The COT does not expect the ossification to be the same in rats and humans.
  - The UF may be to low for ossification at the endpoint
  - Need additional argument for the use of 100 ppm as the POD
  - One option presented by COT was to divide the AEGL-3 value by 3.
- OTHER ISSUES
  - PBPK modeling should be used for interspecies extrapolation and for time scaling
  - Provide justification for not using the Nachreiner (1991, 1992) acute lethality studies for deriving AEGL-3 values.

AEGL-2 DERIVATION

- THE ONLY DATA RELEVANT TO AEGL-2 ARE FROM DEVELOPMENTAL TOXICITY STUDIES

- THIS ANALYSIS INCLUDES AN ADDITIONAL DEVELOPMENTAL TOXICITY STUDY
  - MOUSE STUDY (WELLER ET AL., 2000)
  - SINGLE EXPOSURE TO ETO

AEGL-2 DERIVATION ISSUES

- FOCUS OF THIS PRESENTATION
  - REVIEW CURRENT DERIVATION OF AEGL-2
  - PRESENT SEVERAL ALTERNATIVES FOR DERIVING AEGL-2 VALUES

- CURRENT AEGL-2 VALUES ARE PRESENTED IN THE NEXT TABLE

SNELLINGS ET AL., 1982

Experimental design (exposure time: 6 h/day, GD 6-15, sacrificed GD 20) and evaluation of developmental effects					
Parameters	**0 ppm**	**0 ppm**	**10 ppm**	**33 ppm**	**100 ppm**
# Pregnant females # Viable fetuses/dam	17 9	21 8	20 9	22 8	19 8
Number of litters	21	17	–	–	19
Fetal weight (g) male female	 3.3 ± 0.2 3.0 ± 0.2	 3.4 ± 0.4 3.1 ± 0.3	 3.3 ± 0.3 3.0 ± 0.3	 3.3 ± 0.3 3.1 ± 0.3	 3.1* ± 0.2 2.9* ± 0.1

# fetuses (Litters) exam. 	
.(skeletal)
	
	87 (21)
		
		74 (17)
			
			–
				
				–
					
					75 (19)

Variation, ossification: % affected fetuses (litters) Sternebrae Vertebrae	 7 (29) 1 (6)	 5 (19) 7 (18)	 – –	 – –	 4 (11) 11 (42)

AEGL VALUES IN TSD

Table 1. AEGL 2 Derivation based on decreased fetal body weight and delayed ossification at 100 ppm (Snellings et al., 1982)				
POD = 100 ppm t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
80 ppm	80 ppm	45 ppm	14 ppm	7.9 ppm

AEGL-2 DERIVATION

- Derive AEGL-2 values using the Benchmark Dose (BMD) approach.

- This approach uses all the doses in a study and it is similar to the approach used for AEGL-3.

- The benchmark response (BMR) for derivation of AEGL-2 values is 0.05 ($BMDL_{05}$, same as AEGL-3 derivation).

SNELLINGS ET AL., 1982: BMD APPROACH

AEGL 2 Derivation based on <u>fetal body weight of male rats</u>				
POD = 41 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
33 ppm	33 ppm	18 ppm	5.7 ppm	3.2 ppm

SNELLINGS ET AL., 1982: BMD APPROACH

AEGL 2 Derivation based on <u>fetal body weight of female rats</u>				
POD = 52.7 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
42 ppm	42 ppm	23 ppm	7.4 ppm	4.1 ppm

BBRC, 1993: DATA SUMMARY

Experimental design (exposure time: 6 h/day, GD 6-15, sacrificed GD 21) and evaluation of developmental effects				
Parameters	**0 ppm**	**50 ppm**	**125 ppm**	**250 ppm**
Maternal Effects				
# Pregnant females (Viable fetuses/dam)	23 (9)	20 (9)	21 (8)	24 (8)
weight gain (g) GD 6-15 GD 15-18	 39.18 ± 3.96 35.15 ± 6.55	 32.88 ± 17.95 39.74 ± 14.77	 30.64 ± 9.01* (78) 33.81 ± 8.52	 13.11 ± 11.39** (33) 41.70 ± 7.67** (119)

BBRC, 1993: DATA SUMMARY (CONT.)

Experimental design (exposure time: 6 h/day, GD 6-15, sacrificed GD 21) and evaluation of developmental effects				
Parameters	**0 ppm**	**50 ppm**	**125 ppm**	**250 ppm**
Fetal Effects				
Fetal weight (m&f) (g)	5.161 ± 0.25	4.972 ± 0.277* (96)	4.891 ± 0.27** (95)	4.644 ± 0.29** (90)
Fetal weight (male) (g)	5.312 ± 0.29	5.102 ± 0.29* (96)	5.065 ± 0.30** (95)	4.771 ± 0.30** (90)
Fetal weight (female) (g)	5.010 ± 0.23	4.839 ± 0.259* (97)	4.736 ± 0.29** (95)	4.520 ± 0.28** (90)
# fetuses (Litters) exam.: skeletal	152 (23)	136 (20)	132 (20)	164 (24)

BBRC, 1993: DATA SUMMARY (CONT.)

Experimental design (exposure time: 6 h/day, GD 6-15, sacrificed GD 21) and evaluation of developmental effects				
Parameters	**0 ppm**	**50 ppm**	**125 ppm**	**250 ppm**
Fetuses (litters)				
Interparietal – poorly ossified	19 (9)	23 (12)	32 (13)	88 (23**)
Proximal phalanges - unossified	2 (2)	7 (4)	14 (6)	28 (12**)
Sternebrae #5 - unossified	5 (2)	9 (7)	14 (10**)	17 (10**)
Sternebrae #6 – poorly ossified	0 (0)	3 (2)	7 (6**)	22 (13**)

BRRC, 1993: BMD approach

AEGL 2 derivation based on fetal body weight of male & female rats combined				
POD = 106 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
84 ppm	84 ppm	47 ppm	15 ppm	8.3 ppm

BRRC, 1993: BMD approach

AEGL 2 Derivation based on delayed ossification of sternebrae in male & female rats combined				
POD = 106 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
29 ppm	29 ppm	16 ppm	5.1 ppm	2.8 ppm

SAILLENFAIT ET AL., 1996: DATA SUMMARY

Experimental design (0.5 h or (3 × 0.5 h), GD 6-15, sacrificed GD 21) and evaluation of developmental effects					
Conc. (ppm) & time (h)	**# females exposed**	**# deaths**	**Maternal wt. gain (g)**	**# litters**	**# viable fetuses/ litter**
Maternal Effects					
0 ppm × 0.5 hr	21	0	148 ± 31	18	13.28 ± 3.91
400 ppm × 0.5 h	20	0	157 ± 20	13	14.31 ± 2.39
800 ppm × 0.5 h	20	1	158 ± 25	15	13.20 ± 2.48
1200 ppm × 0.5 h	20	0	143 ± 28	18	13.56 ± 2.53
0 ppm (3 × 0.5 h)	18	0	112 ± 44	12	6.83 ± 6.15
0 ppm (3 × 0.5 h)	21	0	155 ± 25	20	14.70 ± 3.08
200 ppm (3 × 0.5 h)	18	0	131 ± 32	13	10.15 ± 4.36
400 ppm (3 × 0.5 h)	18	0	124 ± 45 (80)	11	10.55 ± 5.30
800 ppm (3 × 0.5 h)	21	0	142 ± 16	18	15.11 ± 2.27
1200 ppm (3 × 0.5 h)	21	0	109 ± 25** 70)	19	13.53 ± 2.89

SAILLENFAIT ET AL., 1996: DATA SUMMARY (CONT.)

Experimental design (0.5 h or (3 × 0.5 h), GD 6-15, sacrificed GD 21) and evaluation of developmental effects				
Conc. (ppm) & time (h)	**Fetal weight (g)**		**variations: # fetuses (litters)**	**fetuses with variations/ litter (%)**
	males	**females**		
0 ppm (0.5 hr)	5.75 ± 0.48	5.41 ± 0.37	14 (9)	15.4 ± 25.4
400 ppm (0.5 h)	5.75 ± 0.25	5.49 ± 0.32	24 (11)	26.9 ± 20.1*
800 ppm (0.5 h)	5.87 ± 0.35	5.64 ± 0.33	20 (9)	23.8 ± 30.3
1200 ppm (0.5 h)	5.70 ± 0.42	5.36 ± 0.38	(59 (16)	47.3 ± 30.8**
0 ppm (3 × 0.5 h)	6.39 ± 0.58	5.85 ± 0.46	10 (8)	47.2 ± 45.9
0 ppm (3 × 0.5 h)	5.79 ± 0.32	5.51 ± 0.31	28 (12)	17.1 ± 21.0
200 ppm (3 × 0.5 h)	5.72 ± 0.66** (90)	5.30 ± 0.46* (91)	4 (3)	4.5 ± 9.8*
400 ppm (3 × 0.5 h)	5.84 ± 0.36	5.56 ± 0.55	8 (4)	14.2 ± 18.6
800 ppm (3 × 0.5 h)	5.43 ± 0.32** (94)	5.13 ± 0.26** (93)	17 (8)	13.0 ± 16.9
1200 ppm (3 × 0.5 h)	5.22 ± 0.42** (90)	4.94 ± 0.40** (90)	16 (6)	12.6 ± 23.8

SAILLENFAIT ET AL., 1996: BMD APPROACH

AEGL 2 Derivation based on fetal body weight of male rats				
POD = 446 ppm ($BMCL_{05}$) t = 90 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
111 ppm	111 ppm	63 ppm	20 ppm	11 ppm

SAILLENFAIT ET AL., 1996): BMD APPROACH

AEGL 2 Derivation based on fetal body weight of female rats				
POD = 450 ppm ($BMCL_{05}$) t = 90 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
112 ppm	112 ppm	63 ppm	20 ppm	11 ppm

WELLER ET AL., 2004: DATA SUMMARY

Experimental design and evaluation of maternal & developmental effects							
Conc. (ppm)	Time (h)	# Exposed (Sperm +)	Maternal Effects				
			# Deaths (%)	Weight Lost (%)	% with Clinical Signs		# with fetuses (%)
					30 min	24 hrs	
0	1.5	50	0	1.2	2.3	0	28 (56)
0	1.75	8	0	0.7	12.5	12.5	6 (75)
0	2	28	1 (3.6)	0.3	0	0	14 (50)
0	3	38	0	3.4	2.6	0	19 (50)
0	6	30	1 (3.3)	3.8	6.7	0	19 (63)
Total		**154**	**2 (1.3)**	**1.9**	**4.8**	**2.5**	**86 (56%)**

WELLER ET AL., 2004: DATA SUMMARY

Conc. (ppm)	Time (h)	# Exposed (Sperm +)	Maternal Effects				
			# Deaths (%)	Weight Lost (%)	% with Clinical Signs		# with fetuses (%)
					30 min	24 hrs	
C × T = 2100 ppm-h							
1400	1.5	39	3 (7.7)	7.2	100.0	20.7	8 (22)
700	3	41	0	6.6	81.6	5.3	22 (54)
350	6	33	0	4.7	53.1	3.1	19 (58)
C × T = 2700 ppm-h							
1800	1.5	73	41 (56.2)	13.0	100.0	66.2	3 (9)
1543	1.75	23	15 (65.2)	13.5	95.7	72.2	1 (13)
1350	2	76	27 (35.5)	11.4	100.0	39.7	7 (14)
900	3	50	1 (2.0)	8.8	98.0	24.0	11 (22)
450	6	41	0 (0)	6.2	95.1	2.4	20 (49)

Summary of AEGL-2 values (ppm)						
Total UF = 10; n = 1.2						
10 min.	**30 min.**	**1 h**	**4 h**	**8 h**	**Comments**	**Reference**
80	80	45	14	7.9	Original values in TSD	Snellings et al., 1982
33	33	18	5.7	3.2	BMD: male fetal rat BW	Snellings et al., 1982
42	42	23	7.4	4.1	BMD: female fetal rat BW	Snellings et al., 1982
84	84	47	15	8.3	BMD: male & female fetal rat BW	BRRC, 1993
29	29	16	5.1	2.8	BMD: delayed ossification, rat	BRRC, 1993
111	111	63	20	11	BMD: male fetal rat BW	Saillenfait et al., 1996
112	112	63	20	11	BMD: female fetal rat BW	Saillenfait et al., 1996
22	22	13	4.0	2.2	BMD eye defects, fetal mouse, 3 h	Weller et al., 2000
40	40	22	7.1	4.0	BMD: eye defects, fetal mouse, 6 h	Weller et al., 2000
206	206	120	36	20	BMD: male & female fetal mouse BW	Weller et al., 2000

WELLER ET AL., 2004: DATA SUMMARY

Experimental design and evaluation of maternal & developmental effects								
Conc. (ppm)	Time (h)	Developmental effects						
		# Implants	# Resorp (%)	# Dead fetuses (%)	Fetal Wt. (g)	C-R leng (mm)	# Fetuses (litters)	Eye Defects # fetuses (litters)
0	1.5	203	28 (13.8)	0	0.92	19.22	175 (28)	13 (6)
0	1.75	50	3 (6.0)	0	0.97	20.03	47 (6)	5 (3)
0	2	95	11 (11.6)	1 (1.1)	0.99	20.70	83 (14)	4 (3)
0	3	141	15 (10.6)	1 (0.7)	0.93	19.71	125 (19)	5 (4)
0	6	150	14 (9.3)	0	0.99	19.52	136 (19)	12 (6)
Total		**639**	**71 (11.1)**	**2 (2.1)**	**0.96**	**19.84**	**566 (86)**	**39 (22)**

WELLER ET AL., 2004: DATA SUMMARY

Experimental design and evaluation of maternal & developmental effects									
Conc. (ppm)	Time (h)	# Exposed[a]	Developmental effects						
			# implants	# Resorp (%)	# dead fetuses (%)	Fetal Wt. (g)	C-R leng (mm)	# offspring (litters)	Eye Defects (offspg/litters)
C × T = 2100 ppm-h									
1400	1.5	39	62	24 (38.7)	17 (27.4)	0.72 (75)	16.89 (85)	21 (8)	7 (3)
700	3	41	168	27 (16.0)	3 (1.8)	0.88 (92)	19.24 (97)	139 (22)	53 (15)
350	6	33	152	13 (8.6)	1 (0.7)	0.97 (101)	19.90 (100)	138 (19)	20 (8)

[a]Sperm +

WELLER ET AL., 2004: DATA SUMMARY

Experimental design and evaluation of maternal & developmental effects									
Conc. (ppm)	Time (h)	# Exposed[a]	Developmental effects						
			# implants	# Resorp (%)	# dead fetuses (%)	Fetal Wt. (g)	C-R leng (mm)	# offspring (litters)	Eye Defects (offspg/litters)
C × T = 2700 ppm-h									
1800	1.5	73	22	14 (63.6)	0	0.70 (73)	16.66 (84)	8 (3)	7 (1)
1543	1.75	23	7	1 (14.3)	0	0.76 (79)	17.83 (90)	6 (1)	6 (1)
1350	2	76	20	9 (45.0)	1 (5.0)	0.86 (90)	18.74 (94)	10 (7)	3 (2)
900	3	50	86	22 (25.6)	5 (5.8)	0.82 (85)	18.42 (93)	59 (11)	34 (9)
450	6	41		28 (18.9)	0	0.97	19.32 (97)	120 (20)	13 (10)

[a]Sperm +

Weller et al., 2000: BMD approach

AEGL 2 Derivation based on fetal eye defects in mice				
POD = 50.5 ppm ($BMCL_{05}$) t = 180 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
22 ppm	22 ppm	13 ppm	4.0 ppm	2.2 ppm

Weller et al., 2000: BMD approach

AEGL 2 Derivation based on fetal eye defects in mice				
POD = 50.5 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
40 ppm	40 ppm	22 ppm	7.1 ppm	4.0 ppm

Weller et al., 2000: BMD approach

AEGL 2 Derivation based on fetal body weight of mice				
POD = 50.5 ppm ($BMCL_{05}$) t = 360 minutes				
Total UF = 10				
n = 1.2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
206 ppm	206 ppm	120 ppm	36 ppm	20 ppm

PBPK MODELING

- Should the NAC/AEGL Committee adopt PBPK modeling for interspecies extrapolation and/or time scaling for AEGL-3 derivation?
- There may be sufficient data for PBPK modeling of ethylene oxide

Should either Nachreiner study be used for deriving AEGL-3 values?

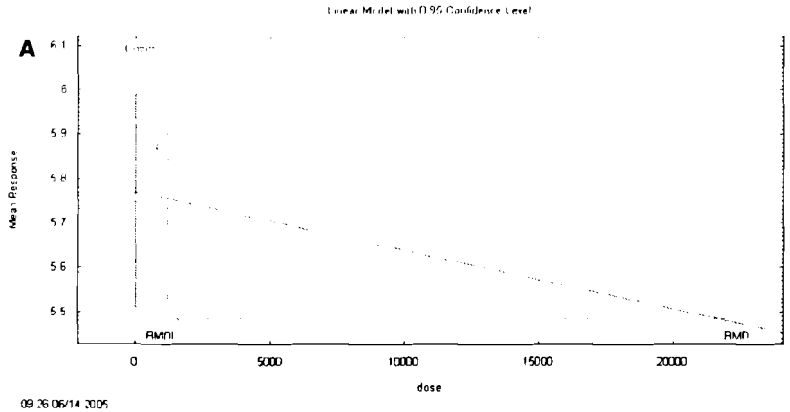
- The Nachreiner studies produce less conservative AEGL values than the Jacobson study
- AEGL values derived from the 1-hr (Nachreiner, 1992) and 4-hr (Nachreiner, 1991) studies are presented below:

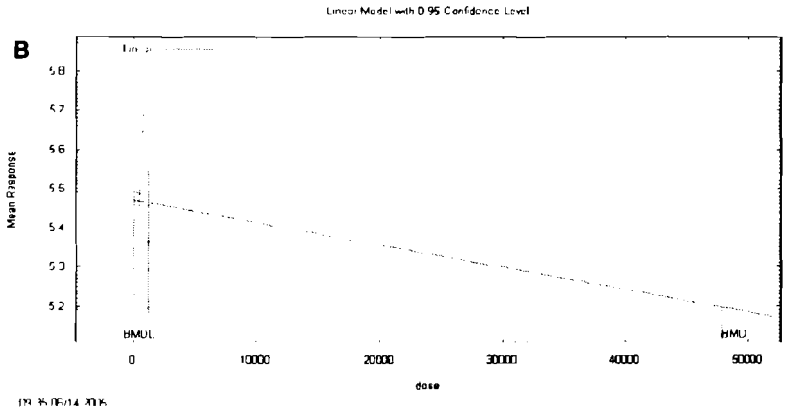
	10 min	30 min	1 hr	4 hrs	8 hrs
Nachreiner, 1992	440 ppm	440 ppm	250 ppm	79 ppm	44 ppm
Nachreiner, 1991	520 ppm	520 ppm	290 ppm	92 ppm	52 ppm
Jacobson et al.	~~206~~ ppm	~~206~~ ppm	~~120~~ ppm	~~36~~ ppm	~~20~~ ppm
	360	360	200	60	35

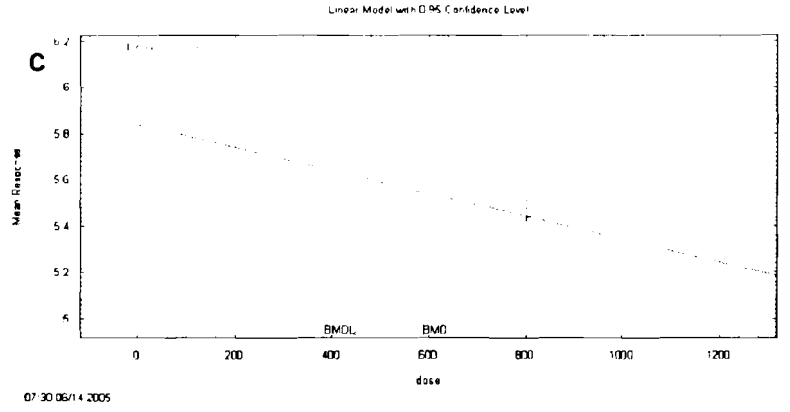
Fetal Weight										
	A	B	C	D	E	F	G	H	I	J
Study:	Saillienfait	Saillienfait	Saillienfait	Saillienfait	BRRC	BRRC	BRRC	BRRC	Dow	Dow
Sex:	Male	Female	Male	Female	Both	Both	Both	Both	Male	Male
Duration:	30 min.	30 min.	90 min.	90 min.	360 min.	360 min.	360 min.	360 min.	360 min.	360 min.
Average Basis:	Dose	Dose	Dose	Dose	Dose/Litter	Fetus/Litter	Resp/Litter	Fetus	Resp/Litter	Dose
Model:	Linear	Linear	Linear	Linear	Linear	Linear	Linear	Linear	Linear	Linear
Degree:	1	1	1	1	1	1	1	1	1	1
Variance:	Constant	Constant	Constant	Constant	Constant	Constant	Constant	Constant	Constant	Constant
Restrict Power:										
BMR:	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
BMR Type:	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev	Rel Dev
BMD	21887.2	47861.8	587.48	592.766	117.525	119.517	119.517	117.53	124.419	124.596
BMDL	1583.24	1688.13	448.569	451.478	88.9884	96.495	96.495	108.044	64.9005	64.7988
AIC Fitted	-50.83369	-61.07328	-57.78951	-66.75648	-82.89154	-137.3957	-137.3957	-1180.634	-143.1983	-146.7595
p-value *	0.4392	0.05395	0.4153	0.1626	0.7709	0.4901	0.4901	0.03124	0.9412	0.9366

* Values > 0.05 preferred

n = litters


A
Linear Model with 0.95 Confidence Level
Mean Response
6.1
6
5.9
5.8
5.7
5.6
5.5
BMDL
BMD
0
5000
10000
15000
20000
dose
09:26 06/14 2005


B
Linear Model with 0.95 Confidence Level
Mean Response
5.8
5.7
5.6
5.5
5.4
5.3
5.2
BMDL
BMD
0
10000
20000
30000
40000
50000
dose


C
Linear Model with 0.95 Confidence Level
Mean Response
6
5.8
5.6
5.4
5.2
BMDL
BMD
0
200
400
600
800
1000
1200
dose
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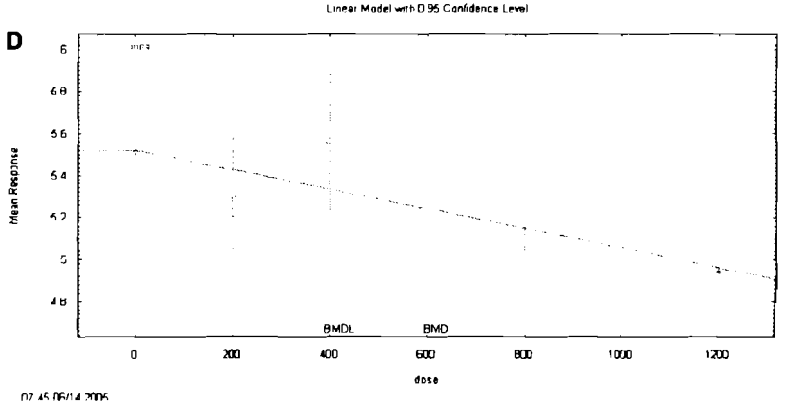
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Linear Model with 0.95 Confidence Level
Mean Response
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5.8
5.6
5.4
5.2
5
4.8
BMDL
BMD
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200
400
600
800
1000
1200
dose
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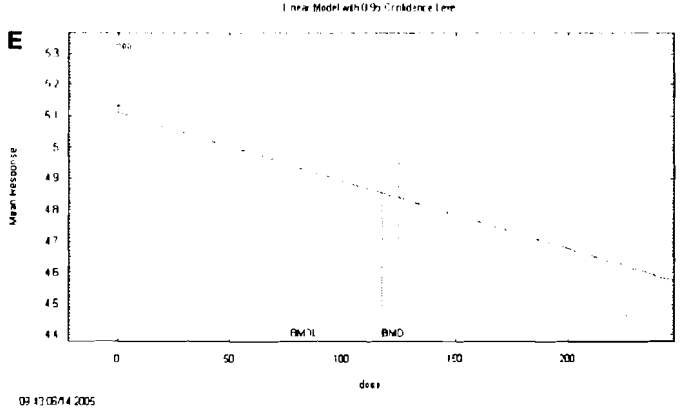
E



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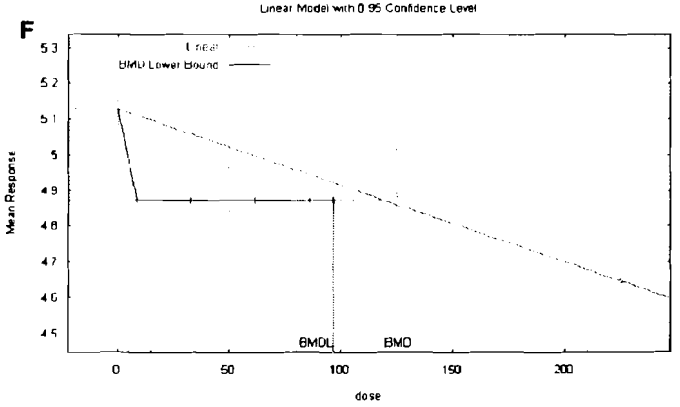

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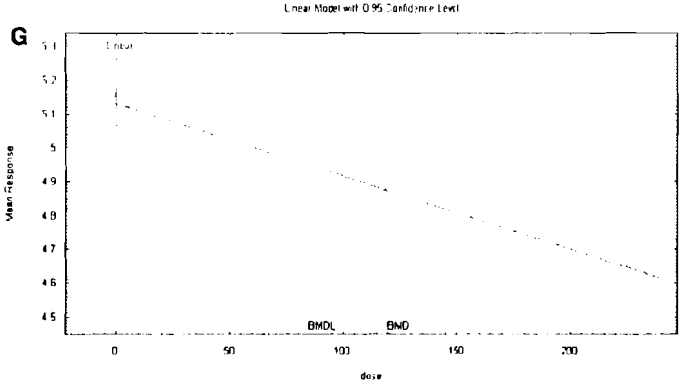

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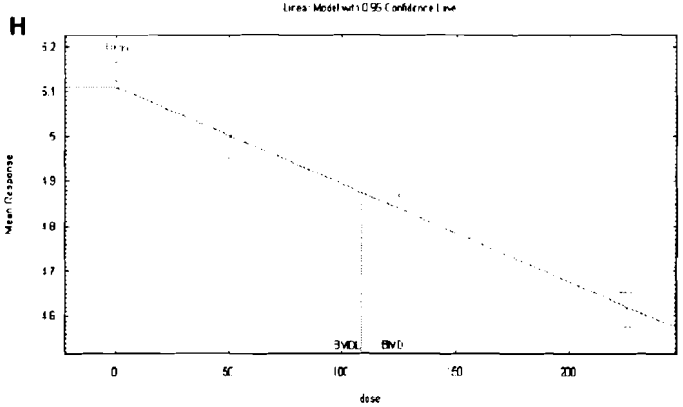

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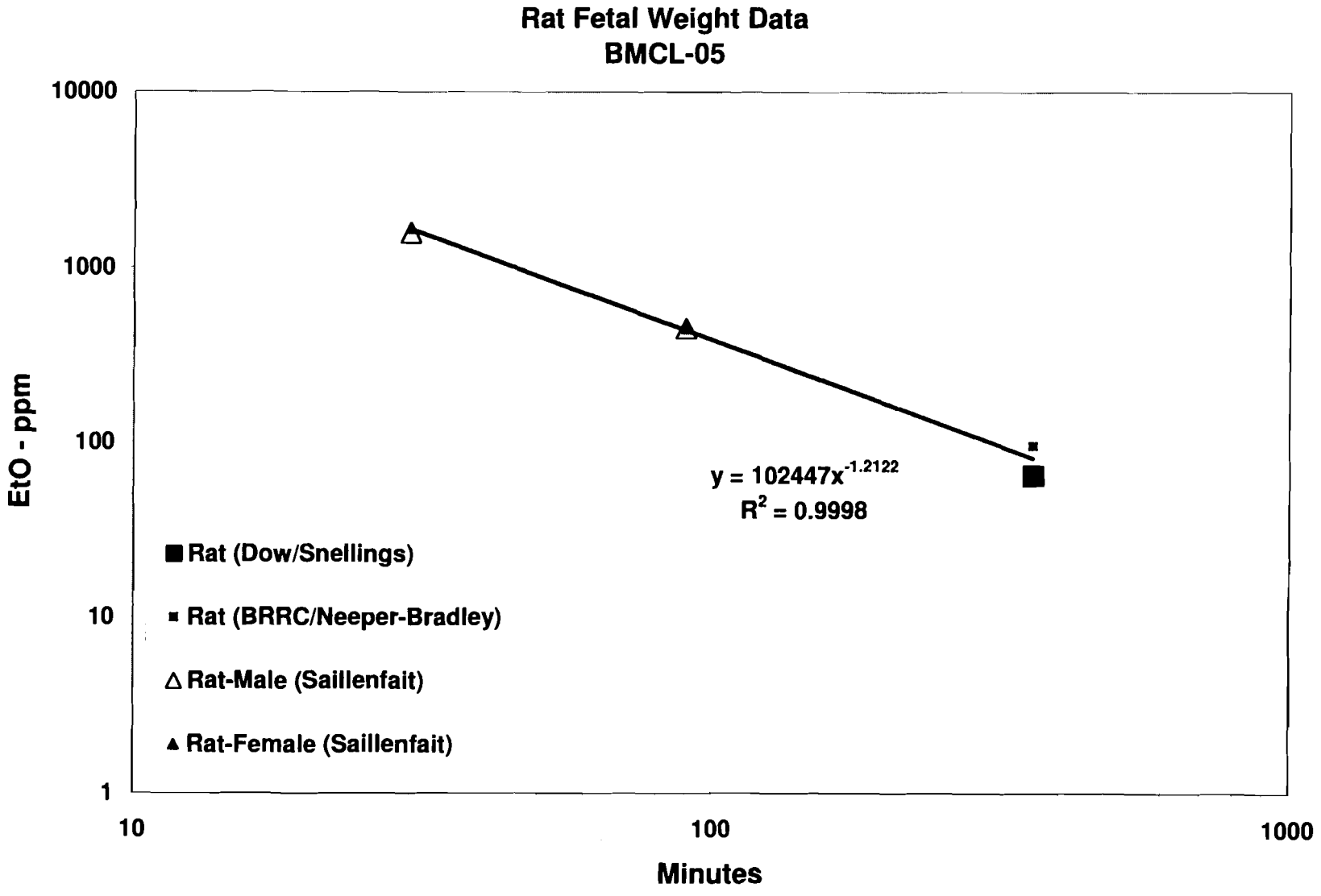
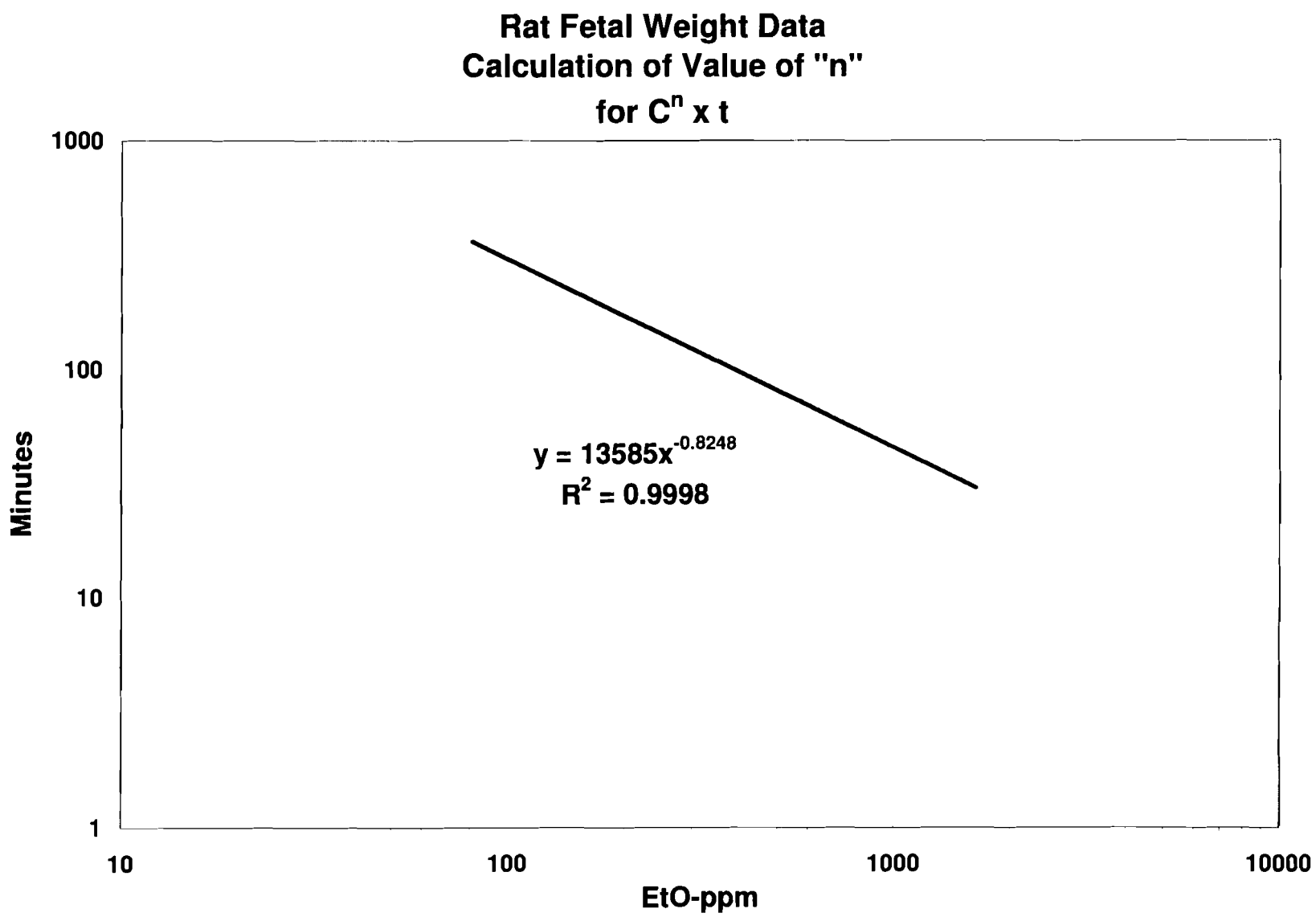
Fetal Weight -- BMCL-05					
Duration (Minutes)	Rat (BRRC/M	Rat (Dow/Snellings)	Rat-Male (Saillenfait)	Rat-Female (Saillenfait)	Rat Average
30			1583.24	1688.13	1636
90			448.569	450.811	450
360	96.495	64.9005			81


Rat Fetal Weight Data
BMCL-05
10000
1000
100
10
1
EtO - ppm
10
100
1000
Minutes
y = 102447x^-1.2122
R^2 = 0.9998
Rat (Dow/Snellings)
Rat (BRRC/Neeper-Bradley)
Rat-Male (Saillenfait)
Rat-Female (Saillenfait)

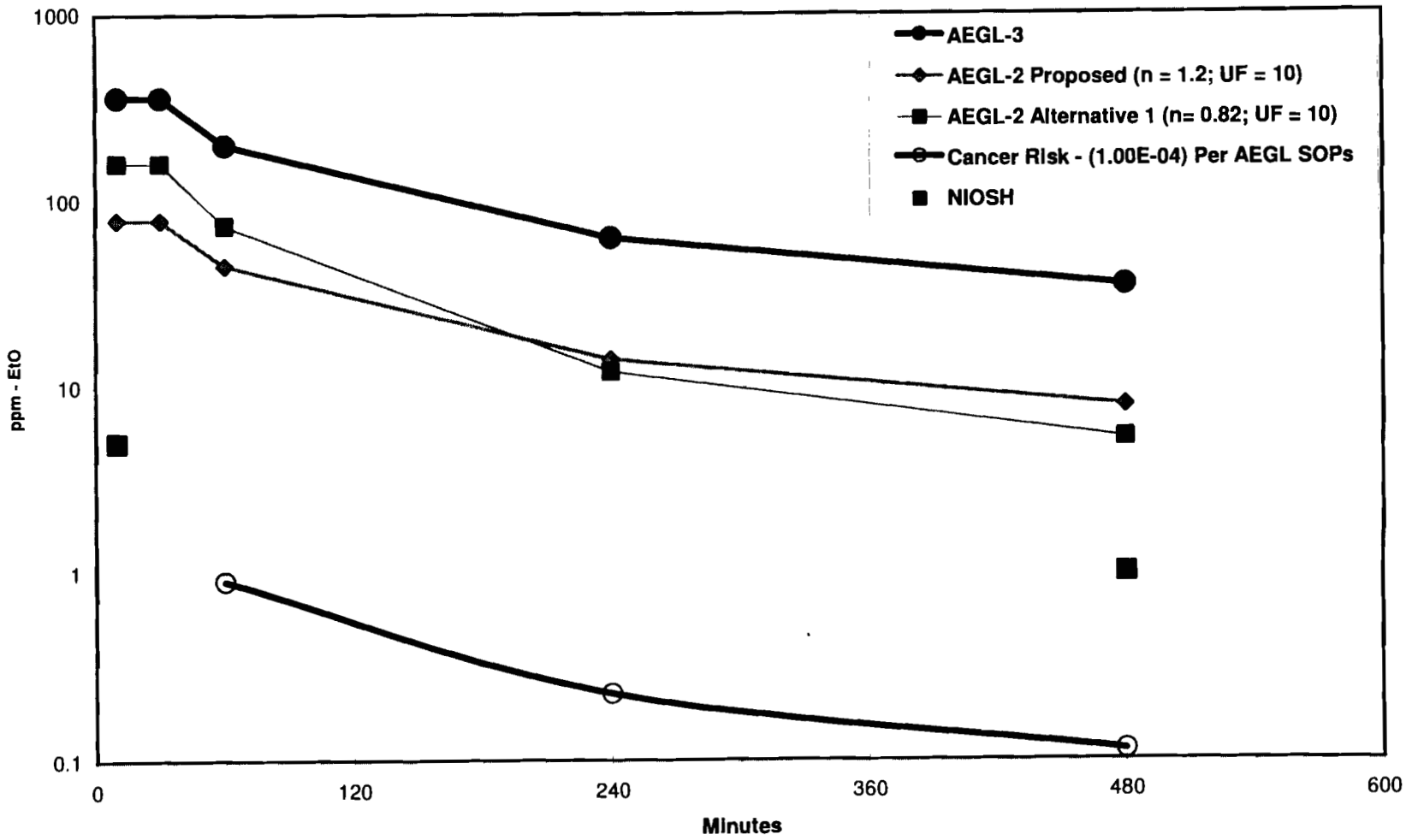

Rat Fetal Weight Data
Calculation of Value of "n"
for C^n x t
1000
100
10
1
Minutes
y = 13585x^-0.8248
R^2 = 0.9998
10
100
1000
10000
EtO-ppm

Chemical: Ethylene Oxide

	Minutes				
Study/Basis for POD	**10**	**30**	**60**	**240**	**480**
AEGL-2 Proposed (n = 1.2; UF = 10)	**79**	**79**	**45**	**14**	**7.9**
Rat BMCL-05 Avg (1636 ppm/30 min)	610	160	65	12	5.3
Rat BMCL-05 Avg (450 ppm/90 min)	630	170	**74**	14	6
Rat BMCL-05 Avg (81 ppm/360 min)	150	150	65	**12**	**5.3**
AEGL-2 Alternative 1 (n= 0.82; UF = 10)	**160**	**160**	**74**	**12**	**5.3**
AEGL-2 Alternative 2 (n= 1.2; UF = 10)	**160**	**160**	**63**	**11**	**6.4**
Cancer Risk - (1.00E-04) Per AEGL SOPs			**0.906971**	**0.226743**	**0.1133714**
Comparisons					
NIOSH	5				1
AEGL-3	360	360	200	63	35

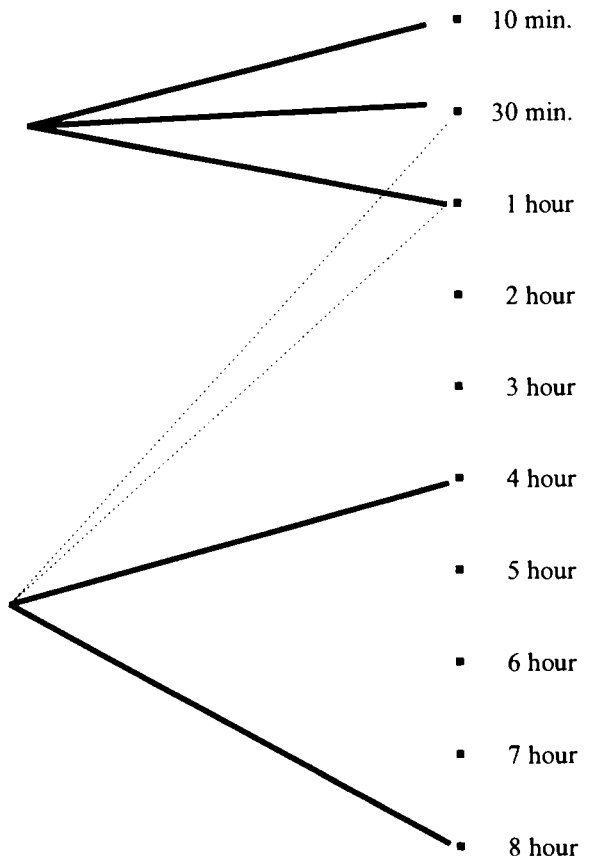
Cancer Slope Value:	0.31	(mg/kg*d)^-1		
Total Daily Exposure (Assuming 70 kg adult):	0.004429	(mg/d)^-1		
Virtually safe exposure level:	8.86E-02	(mg/m^3)^-1		
Acceptable Risk Level:	1.00E-04			
Uncertainty Factor:	6			
Virtualy Safe Lifetime Exposure:	1.48E-06	mg/m^3	2.66E-06	ppm
Safe 24-hour Exposure:	3.78E-02	mg/m^3	6.81E-02	ppm

Proposed & Alternative Ethylene Oxide Reference Values



ATTACHMENT 9

Study	Duration	AEGL Time Intervals
Saillenfait	30 min. exposure	10 min., 30 min., 1 hour
(Endpoint: reduced fetal body wt)		2 hour, 3 hour
Snellings	6 hour exposure	4 hour, 5 hour, 6 hour, 7 hour, 8 hour



Derivation of AEGL-2 Value

Derivation	(Current) Based on Snellings	Based on Saillenfait (0.5h)	(Proposed) Based on Saillenfait/Snellings
$C^n \times t = k$			
effect	< fetal wt. 100 ppm	none (1200 ppm highest)	
t	6 hour	0.5 hour	
n	1.2	1.2	
C	100/10 = 10 ppm	1200/10 = 120 ppm	
k	95.09359155	156.3102651	
10 minutes	80	>300	300
1/2 hour	80	>120	120
1 hour	45	>67	67
4 hour	14	>21	14
8 hour	7.9	>12	7.9
added safety	10 days of exposure	10 days of exposure	10 days of exposure

AEGL-2 values proposed for ethylene oxide

Ethylene Oxide						
Classification	**10 minutes**	**30 minutes**	**1 hour**	**4 hour**	**8 hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	No values derived					
AEGL-2 (Disabling)	**(80) 300**	**(80) 120**	**(45) 67**	**14**	**7.9**	Fetal growth retardation[a]
AEGL-3	**360**	**360**	**200**	**63**	**35**	Lethality

(in parenthesis original value)

Derivation of AEGL-3 Value

	(Current)		Proposed
Derivation	**Based on Jacobson (1956)**	**Based on Nachreiner (1992)**	**Based on Jacobson/Nachreiner**
$C^n \times t = k$			
effect	LC_{01}	LC_{01}	
t	4 hour	1 hour	
n	1.2	1.2	
C	628/10=62.8 ppm	2494/10=24.9 ppm	
k	574.9254897	752.1002603	
10 minutes	360	444*	444*
1/2 hour	360	444	444
1 hour	200	249	249
4 hour	63	79	63
8 hour	35	44	35

* same as 30-min because of uncertainty

AEGL values proposed for ethylene oxide

Ethylene Oxide						
Classification	**10 minutes**	**30 minutes**	**1 hour**	**4 hour**	**8 hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	No values derived					
AEGL-2 (Disabling)	(80) 300	(80) 120	(45) 67	14	7.9	Fetal growth retardation[a]
AEGL-3	(360) 444	(360) 444	(200) 249	63	35	Lethality

(value in parenthesis is the original value)

Summary

- Derivations for shorter time AEGL-2 should consider the Saillenfait 0.5-hour data rather than using 6-hour data for all values

- Derivations for shorter time AEGL-3 should consider the Nachreiner 1.0-hour data rather than using 4-hour data for all values

Weller Paper Should Not Be Used To Evaluate Risk Based On Occular Developmental Effects, Because The Authors State The Following:

- "An interesting observation that requires further study is the relationship between exposure to EtO and the occurrence of micro- and anopthalmia….
- The observations reported in this study are based on a subjective assessment….
- To confirm the presence of an EtO-related effect, further quantitative measurements of the eyes are necessary…."

Commentary Regarding Weller et al. (1999) Fetal Ocular Findings Pursuant to Maternal Ethylene Oxide Exposure

John M. DeSesso

A large number of ocular findings were reported among both treated and control fetuses. Most prevalent finding was microphthalmia (small eyes); also several cases of anophthalmia (missing eyes) were reported among both control and treated groups (only one in controls). These findings, especially anophthalmia, are serious if they are confirmed appropriately. The methods and data reported in the paper suggest that the findings are subjective observations that were not confirmed. The reasons for this suspicion are given below.

Mouse fetuses are very small (usually weighing about 1 gram), which makes them difficult to assess externally. They must be viewed with a magnifying device for detailed observations. Mouse and rat fetuses are born in a relatively immature state and much development occurs after birth. Microphthalmia is particularly hard to assess externally. The orbit develops late in mouse gestation and develops perinatally (shortly before and after birth). When this is combined with the small size of most fetuses, preliminary identification of microphthalmia needs invasive examination to confirm whether the eyeball is missing (a serious condition of anophthalmia) and to determine the state of development of the eyeball and orbit. Moderate microphthalmia is often considered to be a developmental delay that resolves after continued postnatal development. Confirmatory examination usually involves decapitation of fetuses, fixation of head in Bouin's fluid, and coronal free-hand razor sectioning through the orbit; no description of these kinds of procedures was included in the paper.

Overall, the descriptions of the methods used in Weller et al. were internally contradictory and hard to reconcile with reported observations. Importantly, the authors state that tissue samples were removed, including brain and spinal cord. Removal of these structures obviously requires skeletal structures to be destroyed (e.g., skull and vertebral column). Yet authors also claim that all fetuses processed for double staining to visualize osseous and cartilaginous structures of the entire body (including the head) and that the complete skeletal findings were to be the subject of a subsequent paper (not yet published). If the brains were removed, they could have been examined for the presence of intact optic nerves/tracts and the presence of eyeballs. If they were not removed, the alizarin-stained skulls could have had their orbits examined for signs of malformation. Neither type of data was reported in the paper.

Microphthalmia correlates with size of fetuses and (as mentioned above) is often considered to be a manifestation of developmental delay. Indeed, transient microphthalmia (i.e., a condition that resolves due to continued post natal development) is commonly seen in low birth weight mice. Anophthalmia, however, can not resolve after birth due to absence of eyeball. It is not possible to determine whether the diagnoses of anophthalmia are extreme cases of microphthalmia or true absence of the eye without performing the confirmatory evaluations mentioned above. When the combined eye defects data (as percentage of affected fetuses) from all of the control and treated groups in the Weller et al. paper are graphed as a function of mean body weights, there is a strong linear correlation between incidence of ocular defects and smaller mean body weights.

It is not possible to determine the veracity or the biological significance of the ocular findings in mice. However, exposure of pregnant mice to ethylene oxide does appear to cause reduced body weights in fetuses. Because the ocular findings are most commonly reported among those treated groups that had the lower mean body weights, it is likely that the findings are merely due to the small size and developmental delay among the low birth weight fetuses. The data in the Weller et al. paper indicate low body fetal weights in treated groups but are not of sufficient quality to establish the existence or absence of a specific effect of ethylene oxide on ocular development in mice.

RESPONSE TO COT'S COMMENTS FOR ALLYL ALCOHOL

Claudia Troxel

Nancy Kim

Properties:

- Colorless liquid
- Pungent, mustard-like odor

Nonlethal Human Data:

- Odor threshold: range of 1.4 - 2.1 ppm; mean of 1.8 ppm (AIHA, 1989)
- Exposures: 10 volunteers exposed to 2 ppm for 1-3 minutes reported distinct odor but not irritation (Torkelson et al., 1959)

Human sensory response during 5 min. exposure					
Conc. (ppm)	n	Eye irritation		Nose irritation	
		Slight	Severe	Slight	Moderate/ >
0.78	6	0	0	2	0
6.25	6	1	0	3	1
12.5	7	1	0	3	4
25.0	5	0	5	0	5

Dunlap et al., 1958; not stated if nominal/ measured concentrations

Summary of Animal Data

Lethal:

- LC_{50} values (rat; Dunlap et al., 1958):
  1 h -1060 ppm; 4 h -165 ppm; 8 h -76 ppm
  (stated that actual conc. was 15-25% less than nominal)

- NOAEL for lethality (Union Carbide, 1951):
  200 ppm for 1 hr in rats, mice, rabbits
  (no info about controls, methods of exposure, strain or sex of animals, nominal or measured conc, period of observation)

Repeated Exposures

Rat, guinea pig, rabbit (Torkelson et al., 1959)

- 7 (6.6-7.1) ppm : 7 h/d, 5 d/wk, for 28 exp: Reversible liver and kidney damage
- 2 (0.6-3.2) ppm: 7 h/d, 5 d/wk, for ~130 exp: No effects (clinical signs, mortality, body and organ weight, gross and microscopic examination

Rat (Dunlap et al., 1958):

7 h/d, 5 d/wk for 60 exposures:

- 1, 2, 5 ppm: No effects
- 20 ppm: only effect was decreased bw

10 rats/group exposed 7 h/d, 5 d/wk for 60 exposures; Dunlap et al., 1958	
Conc (ppm)	Effect
1, 2, 5	No observable adverse effects
20	Only observable effect ↓ bw
40	Irritation (gone after first few exposures : eye irritation gasping,, nasal discharge); ↑ lung wt
60	1/10 died after 4th exp.; irritation
100	6/10 died during first 46 days; irritation
150	10/10 died: 4 during and 2 following 1st exp; all by 10th exposure; necropsy: hemorrhagic livers, pale/spotted lugs, boated G.I. tracts, congestion of liver/lungs

Metabolism/Mechanism

Acute and repeated inhalation exposures:

Lacrimation, pulmonary edema and congestion; after high conc inflammation and hemorrhage of the liver and kidney.

Histopathology of animals exposed to high conc: pulmonary congestion leading to edema and compensatory emphysema, with degeneration of the cells in convoluted tubules of the kidney, liver, myocardium, ganglion cells of the spinal cord, and retina

Oral or perenteral exposure produces periportal necrosis of liver

Liver necrosis dependent on conversion to acrolein; mediated by cytosolic ADH with NAD^+ ; acrolein detoxified by metabolism to acrylic acid by aldehyde DH or conjugation with GSH

Lung metabolism → glycidol → glycerol; no acrolein because lungs do not contain appreciable amount of ADH

Summary of proposed AEGL values for AllOH					
Level	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	2.1	2.1	2.1	2.1	2.1
AEGL-2	4.2	4.2	4.2	4.2	4.2
AEGL-3	130	130	67	17	8.3

AEGL-1: Slight to moderate irritation in humans at 6.25 ppm for 5 minutes (Dunlap et al., 1958) [UF = 3]

AEGL-2: NOAEL for severe eye irritation in humans exposed at 12.5 ppm for 5 minutes (Dunlap et al., 1958) [UF = 3]

AEGL-3: Highest concentration w/ no mortality in mice, rats, and rabbits of 200 ppm for 1 h (Union Carbide, 1951) [UF = 3]

AEGL-3

- **n value**: derived value of 0.78 based on LC_{50} data from Dunlap et al., 1958; rounded to 1 to be consistent with other chemicals; the 10 min value was set equal to the 30-min value in order not to exceed the 150 ppm conc. that killed almost all the rats only two 7- or 8-hour exposures

- **COT:** NAC has had chemicals with n value of less than 1; rounding to 1 not in SOP

AEGL-3 Total UF of 3

Interspecies UF – 1 because the highest concentration causing no mortality was identical in all three species

Intraspecies UF - 3 because UF of 10 – inconsistent with data; 1, 4, and 8- hour would be 20, 5.1, and 2.5 ppm, respectively.

- Dunlap - rats: 7 hr/d, 5 days/wk for 60 exp. No effects at 1, 2, or 5 ppm; ↓ bw gain at 20 ppm.
- Torkelson - rats, guinea pigs, rabbits, and dogs: no effects at 2 ppm for 7 hr/d, 5 d/wk for 28 exp., reversible liver and kidney damage at 7 ppm for 7 hr/d, 5 d/wk for 134 exp.

COT: AEGL-3 Total UF of 3

- **Interspecies UF – 1** not justified; insufficient data to conclude that all species (including humans) respond similarly to the effects resulting from exposure (suggest UF of 3)

- **Intraspecies UF - 3** It is illogical to make a scientific judgment about what the UF should be based on the data and available information, and if the end result values seem inconsistent with other values, go back and adjust the UFs. The UFs should remain the same and then, if there is a strong reason to change the resulting numbers, an adjustment should be made.

Other possibilities for AEGL-3:

- Use the Dunlap human study:

  25 ppm for 5 min. resulted in severe eye irritation in 5/5 volunteers (endpoint is impaired ability to escape)

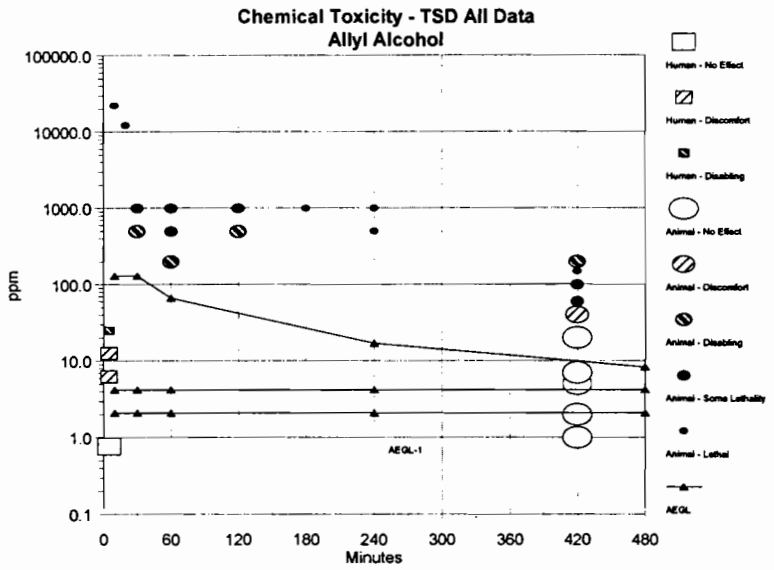
  Total UF of 3: basis of irritation

  Result: 8.3 ppm scaled across time

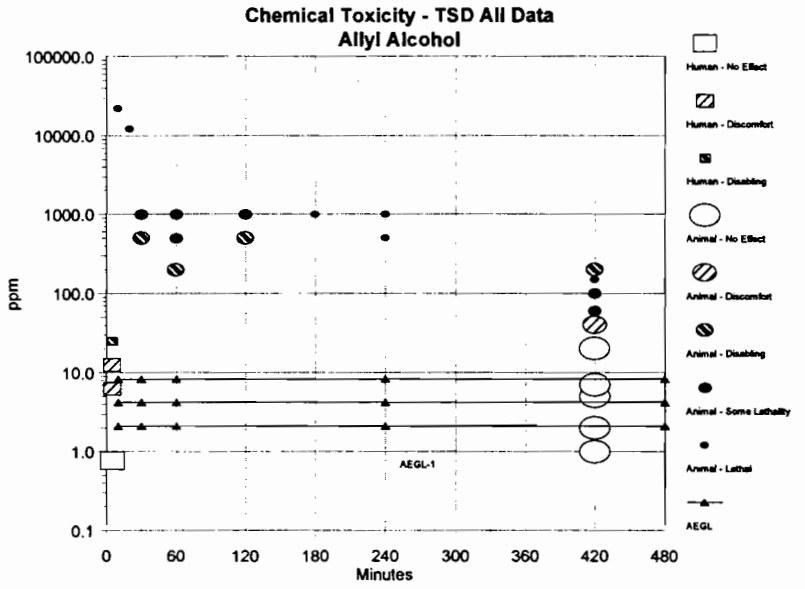
  MF not necessary when value compared to the repeated exposure animal data (1, 2, 5 ppm – no adverse effects)

- Do not derive value

AEGL-1		**2.1**	**2.1**	**2.1**	**2.1**	**2.1**
AEGL-2		**4.2**	**4.2**	**4.2**	**4.2**	**4.2**
AEGL-3						
n	**UF**	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**
-	*3*	*8.3*	*8.3*	*8.3*	*8.3*	*8.3*
1	**3**	**400**	**130**	**67**	**17**	**8.3**
1	10	120	40	20	5	2.5
1	30	40	13	6.7	1.7	0.83
0.8	3	620	160	67	12	5
0.8	10	190	48	20	3.5	1.5
0.8	30	62	16	6.7	1.2	0.5



AEGL-1 and -2 based on human Dunlap data;
AEGL-3 based on animal lethality data



AEGL-1, -2, and -3 based on human Dunlap data

CASE STUDY FOR PBPK MODELING AS APPLIED TO AEGL DERIVATIONS: MIXED XYLENES

Claudia Troxel
Jim Dennison
Bob Benson

The endpoints for the AEGL derivations are as follows:

AEGL-1: Eye irritation in human volunteers exposed to 400 ppm mixed xylenes for 30 min. (Hastings et al., 1986). Because the endpoint is irritation, modeling was not required.

AEGL-2: Rats exposed to 1300 ppm mixed xylenes exhibited poor coordination 2 hr into a 4-hr exposure. This value represents no-effect level for impaired ability to escape (Carpenter et al., 1975).

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

Review:

- Xylenes was reviewed by the COT at the August 2004 meeting. The Interim 1 TSD was based on PBPK modeling applied to AEGL-2 and -3

- Main comment from COT was on use of interspecies UF of 1. Justification based on PBPK modeling, which "eliminated the toxicokinetic component of the uncertainty factor, and the PD component was assigned a 1 based on similar exposure effects (CNS effects) in humans compared to animals." COT stated TSD fails to address the PD aspects of CNS depression across species.

Request to present following scenarios for the xylenes AEGL-2 and -3:

- AEGL values proposed (submitted to Federal Register);
- Using PBPK modeling at rest or at work; with UF applied to:
  - Dose metric (DM; the venous blood concentration [Cv] before plugging into human model);
  - Human equivalent concentration (HEC; value that is produced at end of model prediction);
- Traditional approach (ten Berge time-scaling).

Recommended AEGL-2 and -3 values:

- UF applied to DM
- total UF 3 applied to DM

inter - 3; modeling reduces PK to 1, but 3 remains for PD component

intra - 3 for PK and PD based on MAC; adequate to account for moderate physical activity (not additive - those physically active will not typically be the ones most susceptible)

AF*- 0.3; total UF of 10 drives 8 hr AEGL-2 and -3 values to 108 and 140 ppm, respectively; 150 ppm for 7.5 hr in humans had no effect on performance tests and mild eye irritation

Recommended AEGL values					
Level	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**
AEGL-1	130	130	130	130	130
AEGL-2	2500	1300	920	500	400
AEGL-3	7200	3600	2500	1300	1000

***REQUEST 1*: AEGL values proposed (submitted to the Federal Register):**

- Data indicate that once steady state (SS) is reached, concentration, not duration, is prime determinant in CNS toxicity.
  - AEGL-2 and -3 values set equal across time once SS approached (looked at human venous blood conc. during exposure to 200 ppm, SS appeared to start at ~ 1 hr).
  - one-compartment PK modeling used to extrapolate to exposure durations of 10- and 30-minutes.
  - Total UF of 3: 1 for inter (rats receive greater systemic dose than humans) and 3 for intra (MAC)

Modeling performed by Dr. Gundert-Remy, with following assumptions:

- toxicological endpoint and intensity of effect should be same as observed after exposure to 430 ppm (AEGL-2) or 930 ppm (AEGL-3) for 4 hr;
- concentration and not amount of the substance (AUC) responsible for the effect, qualitatively and quantitatively;
- data from kinetic studies in human volunteers appropriate for further kinetic calculations;
- data of m-xylene were used to represent the mixture of all xylenes;
- kinetics of m-xylene are linear in concentration range under consideration;
- assumed inhalation volume and frequency were constant.

Proposed AEGL values using one-compartment modeling						
Level	**UF**	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**
AEGL-2	3	990	480	430	430	430
AEGL-3	3	2100	1000	930	930	930

Two concerns with this approach

- AEGL-2 derivation based on exposure duration of 4 hr, but effects noted 2-hr into the 4-hr exposure;
- PBPK model developed for xylenes in rats and humans indicate that SS is not reached by 8 hr. Therefore, assumption made in simple one-compartment model that steady-state is reached at 1 hr is probably not correct.

REQUEST 2: **AEGL values generated using PBPK modeling at rest or at work**

- Analysis of UF applied to HEC or DM; total UF of 3

Resting conditions: UF applied to HEC [a] or DM [b]						
UF	**Where UF applied**	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-2						
1	-	7310	3641	2562	1305	1030
3	HEC	2437	1214	854	435	343
3	DM	2512	1284	920	496	403
AEGL-3						
1	-	21,250	10,497	7334	3654	2849
3	HEC	7083	3499	2445	1218	950
3	DM	7162	3571	2512	1280	1011
Ratio of the UF: UF applied to the HEC ÷ UF applied to DM						
3	AEGL-2	0.97	0.95	0.93	0.88	0.85
3	AEGL-3	0.99	0.98	0.97	0.95	0.94

[a] HEC = human equivalent concentration (end of the model prediction)
[b] DM = dose metric (Cv; before plugging into human model)

Work conditions: UF applied to HEC [a] or DM [b]						
UF	**Where UF applied**	**10 min 150 W**	**30 min 145 W**	**1 hr 137 W**	**4 hr 93 W**	**10 min 35 W**
AEGL-2						
1	-	2595	1134	814	673	720
3	HEC	865	378	271	224	240
3	DM	872	386	280	235	262
AEGL-3						
1	-	7610	3312	2368	1948	2051
3	HEC	2537	1104	789	649	684
3	DM	2543	1111	798	660	706
Ratio of the UF: UF applied to the HEC ÷ UF applied to DM						
3	AEGL-2	0.99	0.98	0.97	0.95	0.92
3	AEGL-3	1.00	0.99	0.99	0.98	0.97

[a] HEC = human equivalent concentration (end of the model prediction)
[b] DM = dose metric (Cv; before plugging into human model)

Ratio of work : rest						
AEGL	**10 min**	**30 min**	**1 hr**	**4 hr**	**8 hr**	**Average**
AEGL-2	2.82	3.21	3.15	1.93	1.43	2.78
AEGL-3	2.79	3.17	~~3010~~ 3.10	1.88	1.39	2.73

***REQUEST 3*: The AEGL values using the traditional approach (ten Berge time-scaling):**

The traditional time scaling approach is ten Berge et al. (1986): $C^n \times t = k$. LC_{50} data were available for only 4 and 6 hr, so not appropriate to use these values to derive value of n. Therefore, default values of n = 3 for scaling from longer to shorter durations and an n = 1 for scaling from shorter to longer durations used.

AEGL values using ten Berge time scaling						
Level	**UF**	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**
AEGL-2	3	991	688	546	217	108
AEGL-3	3	2690	1867	1482	933	467

This approach has not been used in the derivation of xylene AEGLs, but is provided for comparison purposes only.

CONCLUSION:

Recommended AEGL-2 and -3 values:

- UF applied to DM
- total UF 3 applied to DM

inter - 3; modeling reduces PK to 1, but 3 remains for PD component

intra - 3 for PK and PD based on MAC; adequate to account for moderate physical activity (not additive - those physically active will not typically be the ones most susceptible)

AF*- 0.3; total UF of 10 drives 8 hr AEGL-2 and -3 values to 108 and 140 ppm, respectively; 150 ppm for 7.5 hr in humans had no effect on performance tests and mild eye irritation

Recommended AEGL values					
Level	**10 m**	**30 m**	**1 h**	**4 h**	**8 h**
AEGL-1	130	130	130	130	130
AEGL-2	2500	1300	920	500	400
AEGL-3	7200	3600	2500	1300	1000

STATUS OF BROMINE

(Questions raised by NRC AEGL Subcommittee)

Problem:

Sparse and conflicting data

- Two data sets
  - Rupp and Henschler 1967
  - Schlagbauer and Henschler 1967 (LC_{50} = 174 ppm)
  - Bitron and Aharonson 1978 (LC_{50} = 424 ppm)
- Data do not agree with each other or other studies
  - These studies not used for chlorine

Data show that chlorine is more toxic than bromine

- LC_{50} values: fluorine > chlorine > bromine

Bromine better scrubbed in upper respiratory tract

- May be more irritating to nasal passages than chlorine

Suggestion:

Base bromine values on chlorine values

Comparison of Bromine AEGL Values with Other Halogens

(Mouse LC_{50} values reflect the toxicity of halogens: fluorine > chlorine > bromine)

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1					
fluorine	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
chlorine	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm
bromine	0.055 ppm	0.033 ppm	0.024 ppm	0.013 ppm	0.0095 ppm
AEGL-2					
fluorine	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
chlorine	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
bromine	0.55 ppm	0.33 ppm	0.24 ppm	0.13 ppm	0.095 ppm
AEGL-3					
fluorine	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
chlorine	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm
bromine	19 ppm	12 ppm	8.5 ppm	4.5 ppm	3.2 ppm

Suggestions:

1. Consider making the bromine AEGL-1 values half of the chlorine values because bromine is better scrubbed in the upper respiratory passages and thus may be more irritating.
2. Consider making the bromine AEGL-2 values equal to, or half of, the chlorine AEGL-2 values (the reasoning for the same values is that bromine is better scrubbed in the upper respiratory tract and will not induce the asthmatic-like attack that occurred with chlorine at 1.0 ppm).
3. Consider making the bromine AEGL-3 values equal to the chlorine AEGL-3 values. This is a conservative approach as bromine is less toxic than chlorine. Alternate suggestion: use the Bitron and Aharonson study: (mouse 30-minute LC_{50} of 424 ppm).

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm	0.25 ppm
AEGL-2	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm
AEGL-3 (LC_{50}/10)	50 ppm	28 ppm 42 ppm	20 ppm	10 ppm	7.1 ppm

Status of Methyl Ethyl Ketone (MEK)
(Questions raised by the National Academy of Sciences AEGL Subcommittee)

Rich data base
- 5 clinical studies
- Human and animal metabolism studies
- Animal toxicity studies

Question of interspecies uncertainty factor of 1
- Metabolism paths are similar in rodents and humans
- Metabolism studies show that uptake is greater in the rodent than in humans
- Pharmacokinetics factor is 0.3-0.7
- Pharmacodynamics factor... no data, ...offset by pharmacokinetic factor
- Combination of pharmacokinetics and pharmacodynamics should be 1

Use of subchronic study for AEGL-2
- AEGL-2 based on effects (lack of narcosis) during the first day
- Use one-fifth of the mean RD_{50} of 10,000 ppm (2000 ppm)

Time-scaling the La Belle and Brieger (1955) rat 4-hour MLE_{01} to shorter time periods
- Values similar to AEGL-2

TABLE 5. Blood Concentrations of Methyl Ethyl Ketone			
Exposure Concentration (ppm)	**Blood Concentration (μg/mL)**	**Exposure Conditions**	**Reference**
Human Subjects			
25 200 400	0.36 6.9 19.4	4 hours, sedentary human subjects	Liira et al. 1990a
Rat[a]			
25 100 300 600	1.0 4.8 25 75	6 hours	Liira et al. 1990a; Liira et al. 1991

[a]Rat whole blood (Liira et al. 1991) was collected following exposures (therefore some metabolism may have taken place); whereas, human samples were collected during exposures. Blood concentrations in humans approached but did not attain steady-state at the end of 4 hours.

Summary of Proposed 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*	2700 ppm	1700 ppm	1700 ppm	Threshold for narcosis - rat (Cavender et al. 1983)
AEGL-3	**	**	4000 ppm*	2500 ppm*	2500 ppm*	Threshold for lethality - mouse, rat (Klimisch 1988; Zakhari 1977; Hansen et al. 1992; La Belle and Brieger 1955)

* The 10- and 30-minute AEGL-2 values and the 1-, 4-, and 8-hour AEGL-3 values are higher than 1/10 of the lower explosive limit (LEL) of methyl ethyl ketone in air (LEL = 18,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

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

HEXAFLUOROACETONE (HFA) AEGL

Update

NAC/AEGL 37
June 13-15, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., NW
Washington DC 20210

HEXAFLUOROACETONE

- **Suggestion at NAC/AEGL 36 to calculate a $BMDL_{05}$ for AEGL-2 development using malformation data from du Pont (1989) rat study.**

- **$BMDL_{05}$ of 1.03 ppm (95% confidence limit) calculated**

- **Because this is essentially the same as the 1.0 ppm initially used to develop the AEGL-2 values which were tentatively approved by majority vote, no adjustment has been made to the proposed values.**

- **The TSD will be revised to reflect the use of the $BMDL_{05}$ assessment in the development of the AEGL-2 values and the uncertainties factors agreed upon at the meeting.**

HEXAFLUOROACETONE

Summary of AEGL Values for Hexafluoroacetone (HFA)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	**NR**	**NR**	**NR**	**NR**	**NR**	**not recommended**
AEGL-2 (Disabling)	**0.40 ppm**	**0.40 ppm**	**0.20 ppm**	**0.050 ppm**	**0.025 ppm**	**absence of developmental effects (malformations) in rats (E. I. du Pont de Nemours & Co. 1989)**
AEGL-3 (Lethality)	**160 ppm**	**160 ppm**	**80 ppm**	**20 ppm**	**10 ppm**	**lethality threshold estimated from rat LC_{50} data (E. I. du Pont de Nemours & Co. 1962a,b)**

NR: not recommended. Absence of AEGL-1 does not imply that exposures below AEGL-2 are without effect.

- AEGL-1 values were not recommended due to insufficient data.

- AEGL-2 values were based upon a NOAEL for malformations in rats: POD of 1.0 ppm for 6 hrs; n=1, interspecies UF of 10 (data for only one laboratory species and no human data) and intraspecies UF of 3 (HFA effects not the result of metabolism, fetus considered a sensitive target; single exposure assumption).

- AEGL-3 value were based upon a NOAEL for lethality in rats: 200 ppm for 4 hrs; n=1, interspecies, UF of 3 (data for two species; metabolism inconsequential) and intraspecies UF of 3 (HFA effects not the result of metabolism).

HEXAFLUOROACETONE

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0071	0.149	0	21	-0.387
0.1000	0.0081	0.162	0	20	-0.4047
1.0000	0.0253	0.581	1	23	0.5568
6.9000	0.8365	20.077	20	24	-0.04249

Chi-square = 0.63 DF = 2 P-value = 0.7315

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1.7489

BMDL = 1.03391

ACUTE EXPOSURE GUIDELINE LEVELS FOR SELECTED METAL PHOSPHIDES

ALUMINUM PHOSPHIDE
POTASSIUM PHOSPHIDE
SODIUM PHOSPHIDE
ZINC PHOSPHIDE
CALCIUM PHOSPHIDE
MAGNESIUM PHOSPHIDE
STRONTIUM PHOSPHIDE
MAGNESIUM ALUMINUM PHOSPHIDE

NAC/AEGL-37
June 13-15, 2005

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Cushmac

Chemical Reviewers: Lynn Beasley and Ernest Falke

- **The metal phosphides are solids.**

- **One mole of <u>aluminum phosphide</u>, <u>potassium phosphide</u>, or <u>sodium phosphide</u> will react rapidly with water or moisture to produce a maximum of one mole of phosphine gas as follows:**

$$AlP + 3H_2O \rightarrow PH_3 + Al(OH)_3$$

$$K_3P + 3H_2O \rightarrow PH_3 + 3KOH$$

$$Na_3P + 3H_2O \rightarrow PH_3 + 3NaOH$$

- **One mole of <u>zinc phosphide</u>, <u>calcium phosphide, magnesium phosphide or strontium</u> phosphide will react rapidly with water or moisture to produce a maximum of two moles of phosphine gas as follows:**

$$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$$

$$Ca_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Ca(OH)_2$$

$$Mg_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Mg(OH)_2$$

$$Sr_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Sr(OH)_2$$

- **One mole of <u>magnesium aluminum phosphide</u> will react rapidly with water or moisture to produce a maximum of three moles of phosphine gas as follows:**

$$Mg_3AlP_3 + 9H_2O \rightarrow 3PH_3 + Al(OH)_3 + 3Mg(OH)_2$$

- **The phosphine gas is responsible for acute toxicity from metal phosphides (studies for Aluminum Phosphide, Zinc Phosphide):**

  Qualitative: similar clinical signs

  Quantitative : phosphine blood levels correlate with severity of clinical signs

  Some inhalation toxicity studies generate phosphine via hydrolysis of solid aluminum phosphide

- **Appropriate chemical-specific data are not available for derivation of AEGL values for metal phosphides.**

- **Phosphine AEGL values have been approved as "final" by COT Subcommittee.**

- **AEGL-1, AEGL-2 and AEGL-3 values for metal phosphides will be based on phosphine AEGL-1, AEGL-2, and AEGL-3 values, respectively, using a molar equivalence approach.**

- **AEGL values for metal phosphides will be expressed as ppm or mg/m^3 phosphine.**

- **Aluminum Phosphide, Potassium Phosphide, and Sodium Phosphide:**

  Phosphine AEGL values will be adopted as AEGL values for aluminum phosphide, potassium phosphide, and sodium phosphide, because one mole of phosphine is produced for each mole of aluminum phosphide, potassium phosphide, or sodium phosphide hydrolyzed.

- **Zinc Phopshide, Calcium Phosphide, Magnesium Phosphide, and Strontium Phosphide:**

  Phosphine AEGL values will be divided by a molar adjustment factor of 2 to approximate AEGL values for zinc phosphide, calcium phosphide, magnesium phosphide, and strontium phosphide, because a maximum of two moles of phosphine may be produced for each mole of zinc phosphide, calcium phosphide, magnesium phosphide, or strontium phosphide hydrolyzed.

- **Magnesium Aluminum Phosphide:**

  Phosphine AEGL values will be divided by a molar adjustment factor of 3 to approximate AEGL values for magnesium aluminum phosphide, because a maximum of three moles of phosphine may be produced for each mole of magnesium aluminum phosphide hydrolyzed.

Hydrolysis of Metal Phosphides				
Metal Phosphide	**Hydrolysis Reaction**	**Moles Phosphine**	**Phosphine evolution rate @ 20°C and 1 atm (ml/kg·min)**	**Time to 100% hydrolysis (min)**
Aluminum Phosphide	$AlP + 3H_2O \rightarrow PH_3 + Al(OH)_3$	1	2069.7	20
Potassium Phosphide	$K_3P + 3H_2O \rightarrow PH_3 + 3KOH$	1	807.6	120
Sodium Phosphide	$Na_3P + 3H_2O \rightarrow PH_3 + 3NaOH$	1	997.8	66
Zinc Phosphide	$Zn_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Zn(OH)_2$	2	929.9	180
Calcium Phosphide	$Ca_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Ca(OH)_2$	2	1274.6	94
Magnesium Phosphide	$Mg_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Mg(OH)_2$	2	1781.4	50
Strontium Phosphide	$Sr_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Sr(OH)_2$	2	737.1	290
Magnesium Aluminum Phosphide	$Mg_3AlP_3 + 9H_2O \rightarrow 3PH_3 + Al(OH)_3 + 3Mg(OH)_2$	3	1865.2	68

RELATIONAL COMPARISON OF AEGL VALUES FOR METAL PHOSPHIDES*
(EXPRESSED AS PPM OR MG/M^3 PHOSPHINE)

Compound(s)	Classification	10-min	30-min	1-hr	4-hr	8-hr
Aluminum Phosphide	**AEGL-1**	NR	NR	NR	NR	NR
Potassium Phosphide	**AEGL-2**	4.0 ppm (5.6 mg/m^3)	4.0 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.50 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)
Sodium Phosphide	**AEGL-3**	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.90 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)
Zinc Phosphide	**AEGL-1**	NR	NR	NR	NR	NR
Calcium Phosphide	**AEGL-2**	2.0 ppm (2.8 mg/m^3)	2.0 ppm (2.8 mg/m^3)	1.0 ppm (1.4 mg/m^3)	0.25 ppm (0.36 mg/m^3)	0.13 ppm (0.19 mg/m^3)
Magnesium Phosphide	**AEGL-3**	3.6 ppm (5.0 mg/m^3)	3.6 ppm (5.0 mg/m^3)	1.8 ppm (2.6 mg/m^3)	0.45 ppm (0.65 mg/m^3)	0.23 ppm (0.32 mg/m^3)
Strontium Phosphide						
Magnesium Aluminum Phosphide	**AEGL-1**	NR	NR	NR	NR	NR
	AEGL-2	1.3 ppm (1.9 mg/m^3)	1.3 ppm (1.9 mg/m^3)	0.67 ppm (0.93 mg/m^3)	0.17 ppm (0.24 mg/m^3)	0.08 ppm (0.12 mg/m^3)
	AEGL-3	2.4 ppm (3.3 mg/m^3)	2.4 ppm (3.3 mg/m^3)	1.2 ppm (1.7 mg/m^3)	0.30 ppm (0.43 mg/m^3)	0.15 ppm (0.21 mg/m^3)

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

DIMETHYLAMINE

(**CAS Reg. No.** 124-40-3)

RIHTOP Staff Scientist: Alexander A. Maslennikov

Chemical Manager: Ernie Falke

Table 1 – Draft AEGLs for Dimethylamine approved by NAC/AEGL Committee

AEGL-1 100 ppm UF=10

AEGL-3 2500 ppm UF=10 n=3 (↓); n=1 (↑)

Table 1. Summary of AEGL Values.					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (No disabling)	10 ppm 19 (mg/m^3)	10 ppm 19 (mg/m^3)	10 ppm 19 (mg/m^3)	10 ppm 19 (mg/m^3)	10 ppm 19 (mg/m^3)
AEGL-2 (Disabling)	39 ppm 72 (mg/m^3)	39 ppm 72 (mg/m^3)	31 ppm 57 (mg/m^3)	20 ppm 37 (mg/m^3)	13 ppm 24 (mg/m^3)
AEGL-3 (Lethality)	570 ppm 1,050 (mg/m^3)	570 ppm 1,050 (mg/m^3)	450 ppm 830 (mg/m^3)	290 ppm 540 (mg/m^3)	190 ppm 350 (mg/m^3)

(AEGL-2 175ppm UF=10 n=3 (↓); n=1 (↑) was presented, but wasn't discussed

Table 2. Summary of Nonlethal Inhalation Data on Laboratory Animals				
Species	**Concentration (ppm)**	**Exposure Time**	**Effect**	**References**
Rats	175	6-hour	Discharge of modified mucus, erosion and fenestration of anterior edges in the septum	Gross et al., 1987
Rabbits / Guinea Pigs	185	20 weeks	Central lobular degeneration	Hollingsworth, R.L. and Rowe, V. K., 1964
	97		Reversible inflammation in olfactory and sensory cells	
Rats / Mice	100	10-min	Inhibition of respiratory rate in animals by 15%	Steinhagen et al., 1982
Rats / Mice	175	2 years	Inflammation and epithelial hyperplasia in the respiratory mucous	Buckley L.A. et al., 1985
	50		Reversible minimal changes in olfactory mucous	
	10		Certain insignificant olfactory changes	
Mice	50	12 months	Reversible inflammation signs on the side of nasal pass ways	Gross E.A. et al., 1987
Rats	100	90 days	Slight body weight loss in the first week	CIIT, 1982
	30			
	10		No visible changes	

Table 3 - AEGL-2 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
78 ppm ($140\ mg/m^3$)	49 ppm ($91\ mg/m^3$)	37 ppm ($68\ mg/m^3$)	21 ppm ($38\ mg/m^3$)	16 ppm ($29\ mg/m^3$)

Derivation of AEGL-2

Key Study: Gross et al. (1987). Single 6-hour exposure of male rats to dimethylamine at 175 ppm concentration caused a wide spectrum of disorders from epithelial vacuolization to ulceration and acute or chronic inflammation. No irreversible histological disorders were observed.

Toxicity Endpoint: Increase of DMA chronic inhalation exposure level up to 185 ppm concentration caused clinical signs in the form of central lobular degeneration (Hollingsworth and Rowe, 1964). Lowering the level of chronic DMA inhalation exposure of rats at (100 ppm) did not lead to any histopathological changes (CIIT, 1982).

Uncertainty Factors: To account for interspecies variability of DMA induced rhinitis, erosion of anterior edges, and fenestration of limiting layer an uncertainty factor of 3 was used. UF 10 was used to account for intraspecies variability. Based upon an evaluation of the supporting data an Adjustment Factor of 1/3 was used to give a Total UF of 10.

Time scaling: Values were time scaled from the 6 hour data using a value of $n = 2.4$. Time scaling was performed to 10 minutes even though the point of departure was a 6 hour exposure because the value of n was derived from data which ranged from 6 minutes to 6 hours.

Table 4 - AEGL-1 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
1 ppm ($1.9\ mg/m^3$)	1 ppm ($1.9\ mg/m^3$)	1 ppm ($1.9\ mg/m^3$)	1 ppm ($1.9\ mg/m^3$)	1 ppm ($1.9\ mg/m^3$)

Derivation of AEGL-1

Key Study:	Buckley et al., 1985; CIIT, 1982 - 1983. Mice and rats were exposed to 10 ppm for 6 hours per day, 5 days per week for 2 years. Interim sacrifices were made at 6, 12, and 18 months. At the 6 month sacrifice no lesions were found in the olfactory epithelium of rats exposed to 10 ppm and equivocal olfactory changes in mice.
Toxicity Endpoint:	Increasing of chronic exposure level (50 ppm) caused destruction of the olfactory epithelial sensory cells and degeneration of the olfactory nerves.
Uncertainty Factors:	In order to account for interspecies variability an uncertainty factor of 3 was used. UF 3 was used to account for intraspecies variability.
Scaling Process:	was not done
Time Scaling:	was not done

Table 5. LC_{50} Values				
Citation	Species	Duration of Exposure minutes	2-day LC_{50} Calculated from data with EPA software	14-day LC_{50} Calculated from data with EPA software
Uhlrich et al., 1994	rat – Sprague Dawley – male and female	6	-	17,649
		20	-	7,341
		60	-	5,285
Mezentseva, 1956	mouse	120	7,560	4,595
Steinhagen et al., 1982	rat – Fiscer-344 male	360	4,540 Steinhagen et al, 1982 calculation	2,759 calculated by multiplying 4,540 (4,595/7,650)

Table 6 - AEGL-5 Values for Dimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
560 ppm (1,000 mg/m^3)	350 ppm (650 mg/m^3)	260 ppm (490 mg/m^3)	150 ppm (270 mg/m^3)	110 ppm (200 mg/m^3)

Derivation of AEGL-3

Key Study: Mezentseva (1956) conducted research to determine LC_{50} for DMA in mice. For this purpose few groups of animals were subjected to 2-hour exposure at concentrations ranging between 800 ppm and 26,000 ppm with further 14-day period of observation. (Factual data were not provided). Although it was not stated whether LC50 was determined, this value was computed by other authors (Steinhagen et al., 1982) and it was derived at 7,560 ppm and 4,725 ppm accordingly for 48-hour and 14-day observations respectively.
$BMCL_{05}$ of **1978 ppm** with a 2 hour exposure in mice

Uncertainty Factors: Based on LC50 values an uncertainty factor of 3 was used to account for interspecies variability of DMA induced toxicity. Intraspecies variability was limited by a factor of 10. Based upon an evaluation of the supporting data an Adjustment Factor of 1/3 was used to give a Total UF of 10

Time scaling: Values were time scaled from the 2 hour data using a value of n = 2.4.

Table 7. Values of n Derived with Using of Different Combinations of 14 day LC_{50} Data Sources

Data source	Species	Exposure duration range in minutes	Value of n
Uhlrich et al., 1994 as cited in ERPG, 2004	rat	6-60	1.9
Uhlrich et al., 1994 and Mezentseva, 1956	rat and mouse	6-120	2.26
Uhlrich et al., 1994 and Steinhagen, 1982	rat	6-360	2.3
Uhlrich et al., 1994 and Mezentseva, 1956 and Steinhagen, 1982	rat and mouse	6-360	2.36 (rounded up to 2.4 for n)

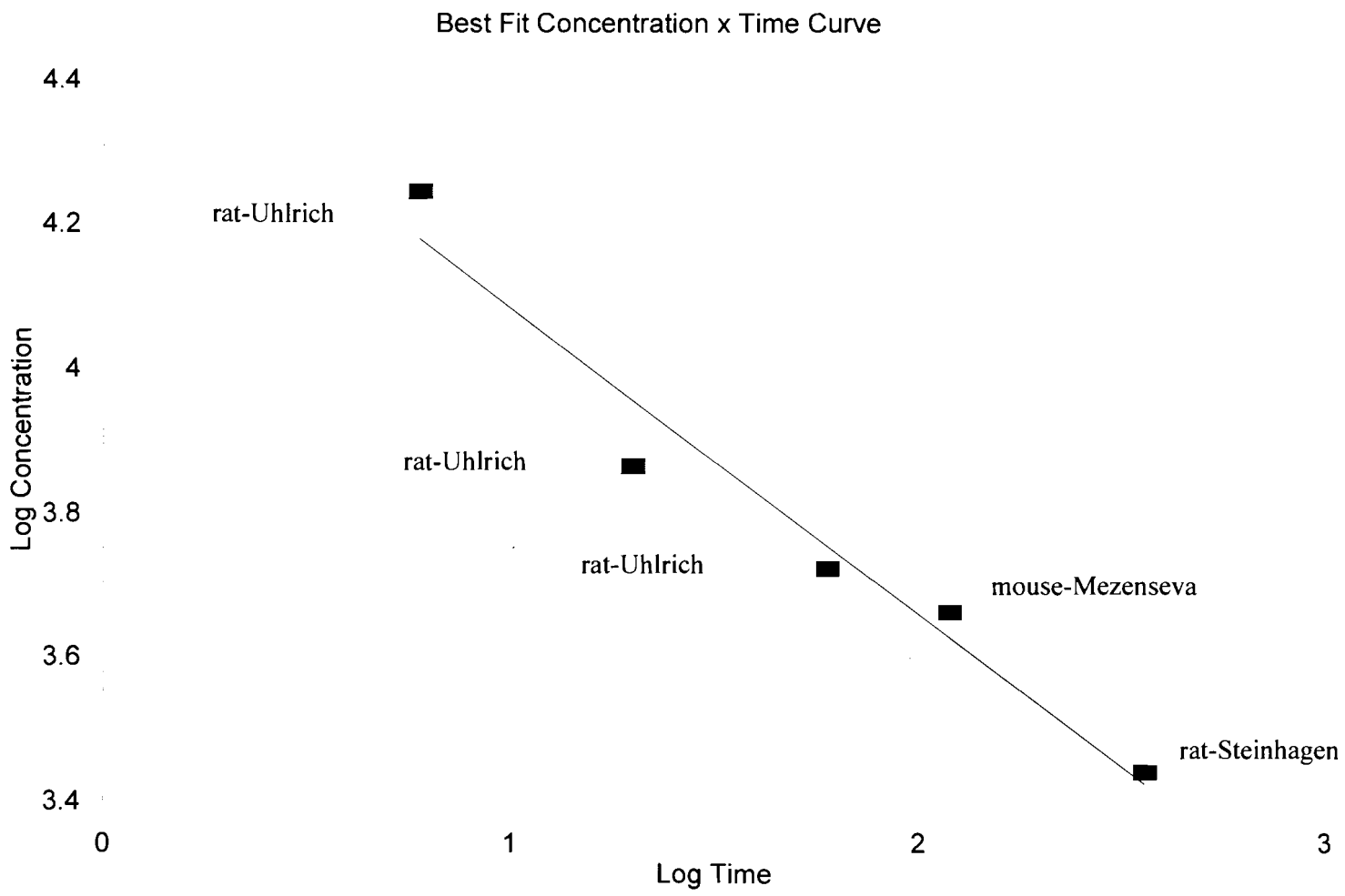
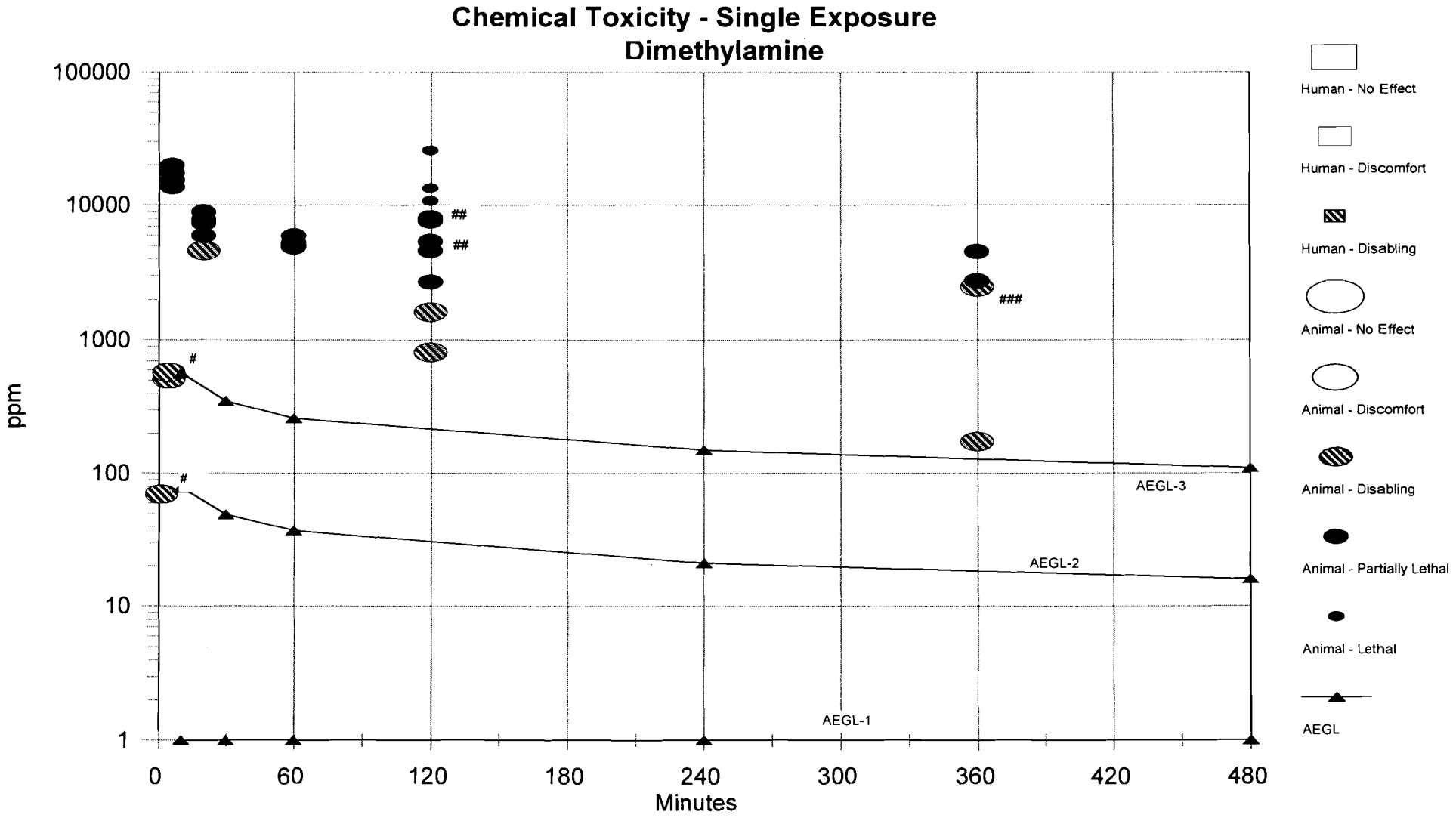


Figure 1. Value of n = 2.36 derived with using of pooled data of Ulrich, Mezentseva, and Steinhagen

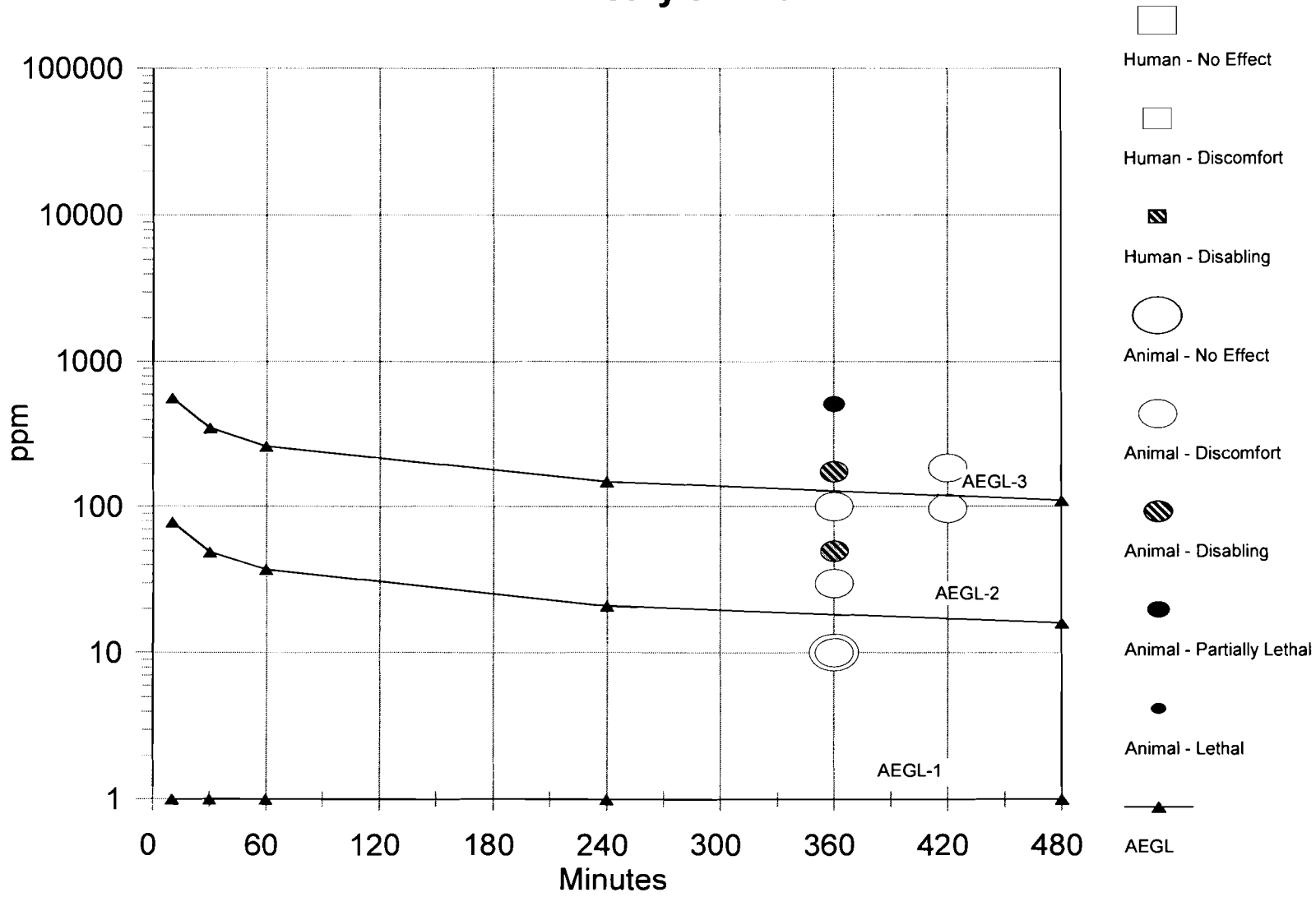


The data at 1 and 4.5 minutes are RD50 values from 2 studies. The 70 ppm RD50 was performed with Swiss OF1 mice. The 511 and 573 ppm values were performed in Swiss Webster mice and rats respectively.

LC50 values of 7650 ppm with 2 hours of exposure and 4540 ppm with 6 hours of exposure are based upon a 2 day observation period. The LC50 for the 120 minute study with a 14 day observation period was 4595 ppm.

Although no rats died at 2500 ppm with 6 hours of exposure with a 48 hour observation period, the authors stated that the effects were so severe that some probably would have died with a 14 day observation period.

Chemical Toxicity - Multiple Exposure
Dimethylamine



Proposed AEGLs for Dimethylamine

AEGL-1 10 ppm UF=10

AEGL-2 175 ppm UF=10 n=2.4

AEGL-3 1978 ppm UF=10 n=2.4

Table 8. Summery of AEGL Values.

Classification	Exposure Duration				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (No disabling)	1 ppm (1.9 mg/m^3)	1 ppm (1.9 mg/m^3)	1 ppm (1.9 mg/m^3)	1 ppm (1.9 mg/m^3)	1 ppm (1.9 mg/m^3)
AEGL-2 (Disabling)	78 ppm (140 mg/m^3)	49 ppm (91 mg/m^3)	37 ppm (68 mg/m^3)	21 ppm (38 mg/m^3)	16 ppm (29 mg/m^3)
AEGL-3 (Lethality)	560 ppm (1,000 mg/m^3)	350 ppm (650 mg/m^3)	260 ppm (490 mg/m^3)	150 ppm (270 mg/m^3)	110 ppm (200 mg/m^3)

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYLAMINE (CAS NO. 74-89-5)

$CH_3–NH_2$

PRESENTED by:

CHEMICAL MANAGER
MARQUEA D. KING, PH.D.
U.S. EPA

ON BEHALF of:

LYUDMILA TOCHILKINA
RESEARCH INSTITUTE OF HYGIENE, TOXICOLOGY AND OCCUPATIONAL PATHOLOGY
(RIIITOP), RUSSIA

NAC/AEGL MEETING, Washington, DC
JUNE 13-15, 2005

Monomethylamine (MMA) – a primary aliphatic amine

➢ **Main use:**

In organic synthesis, as a fuel additive, in the manufacture of pharmaceutical preparations, insecticides, surfactants, explosives, plastic monomers, ion exchange resins, rubber accelerates, cellulose acetate rayon, photographic developers, and also in the tanning and dyeing industries

➢ **U.S. production:**

1981 – 48 million lbs
1988 – 195 million lb
1997 – 318 million pounds

Physical and Chemical Properties of Methylamine

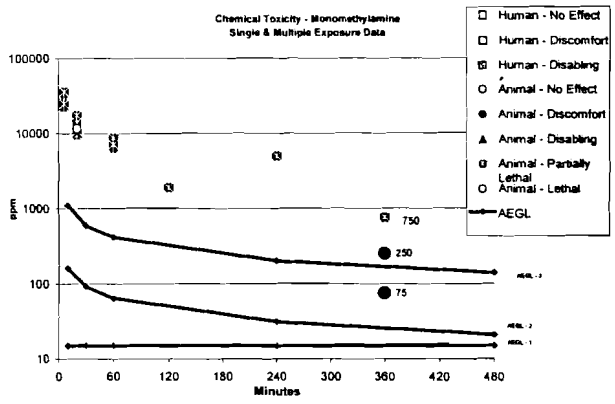
PARAMETER	VALUE
Physical State	Colorless readily liquefied gas
Solubility	Soluble in water and organic solvents
Coefficient water/oil distribution	0.16 – 0.27; 0.71 log Pow
Basicity	Stronger base than ammonia: pk_b =3.35, pk_a =10.65 (25°C)
Stability	Stable
Vapor Pressure	2 atm (25°C)
Vapor Density	1.07 (Air =1); 1.32 kg/m³ (0.082 lb/ft³)
Specific Volume	12.1 ft³/lb
Boiling Point	-6.3°C (-136.3°F) @ 1 atm: -16.6°C (61.8°F)
Flash Point	0°C (32°F)
Auto-Ignition Temperature	430°C
Explosive Limits	4.9 to 20.7 vol% in air
Melting Point	-93°C – -93.5°C (-136°F – -136.3°F)
Incompatibility	Most metals (mercury!), acids, strong oxidizers
Calculation Factors	**1 ppm = 1.27 mg/m³;** **1 mg/l=783 ppm**

Characteristics:

- Strong lachrymator
- Irritant for skin and mucous membranes
- Target organs: Liver and Lungs
- Halo vision at low inhalation concentration (reversible)
- Corneal damage (burns/frostbite) during liquid exposure (sometimes irreversible)
- Pungent smell of gas mixed with fish or ammonia
  - o Readily detectable at 10 ppm
  - o Strong at 20-100 ppm
  - o Intolerable at 100-500 ppm
- Threshold is: **0.0009 - 4.68 ppm**
- Irritation threshold: **7.9 ppm**

ACUTE INHALATION TOXICITY

Species	Concentration (ppm)	Exposure Time (min)	Effect	Reference
Rat	4,892	240	LC_{50}	Koch F. et al., 1980
Rat	448	150	LC_{50}	Sarkar S. N. et al., 1992
Rat	24,400	6	LC_{50}	**Air Products and Chemicals, 1992**
Rat	9,600	20	LC_{50}	Ulrich, et al., 1994
Rat	7,110	60	LC_{50}	Bisson M. et al., 2003
Rat	5,290	60	LC_{50}	Airgas, MSDS, 1996
Rat	5,000	60	LC_{50}	BOC gases, MSDS, 1995
Rat	7,000	60	LC_{50}	AIR LIQUIDE S.A., 2002
Mouse	1,890	120	LC_{50}	Gorbachev E.M., 1957



AEGL-3

Key reference:

Air Products and Chemicals, 1992

Results from:

- Ulrich, C.E. et al. (1994). Acute Inhalation of Five Aliphatic Amines (abstract). The Toxicologist, 14(1)1214 – Details Per Society of Toxicology Meeting Poster (1994) and Personal Communication from B.Z. Drozdowicz (Air Products (2003).

- Bisson M., Tissot S., Pichard A. The Thresholds of Acute Toxicity of Methylamine (CH_3NH_2) = Seuils de Toxicité Aiguë Méthylamine (CH_3NH_2). INSTITUT NATIONAL DE L'ENVIRONNEMENT INDUSTRIEL ET DES RISQUES (INERIS): Rapport Final, 2003. – 24 P =

Provide coinciding mortality data

Acute Inhalation Mortality Data on Methyl Amine: Mortality Tables extracted from 1992 studies conducted for Air Products by IRDC (today's MPI)

Mortality Data from Single Exposure Rat Inhalation Study

Exposure Duration (min)	Group Number	Actual Concentration (ppm)	Number of Deaths/ Number on Study
6	V	**17,600**	**0/10**
	VI	22,500	3/10
	VII	35,300	9/10
	X	26,500	6/10
	XII	26,200	9/10
20	VIII	17,400	9/10
	IX	10,600	3/10
	XI	13,900	8/10
	XIII	11,600	10/10
	XV	11,000	6/10
	XVI	10,800	7/10
60	XIV	8,670	9/10
	XVII	**4,100**	**0/10**
	XVIII	6,370	2/10
	XIX	7,000	4/10
	XX	7,100	6/10

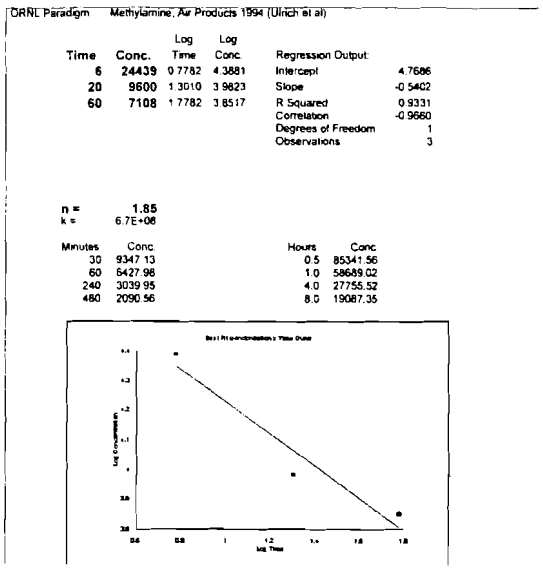
BMD Analysis on Air Products and Chemicals, 1992 {Ulrich, et al., 1994}

6 minutes	BMD_{01}	$BMDL_{01}$	BMD_{05}	$BMDL_{05}$	**BMD_{50}**	$BMDL_{50}$	1/3 LC_{50}
Forced zero	15502	11380	17713	14067	**24439**	22597	7532

20 minutes	BMD_{01}	$BMDL_{01}$	BMD_{05}	$BMDL_{05}$	**BMD_{50}**	$BMDL_{50}$	1/3 LC_{50}
Forced zero	3829	183	5012	489	**9600**	5117	1706

60 minutes	BMD_{01}	$BMDL_{01}$	BMD_{05}	$BMDL_{05}$	**BMD_{50}**	$BMDL_{50}$	1/3 LC_{50}
Forced zero	5076	3731	5602	4482	**7108**	6703	2234

LC_{50}/Derivation of n – rat data only



n = 1.9

AEGL-3 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
1100 ppm (1400 mg/m³)	590 ppm (750 mg/m³)	410 ppm (520 mg/m³)	200 ppm (250 mg/m³)	140 ppm (180 mg/m³)

Tested species/Strains/Number: Male and female rats of CD line, 5/group/sex

Effects:
24,439 ppm - LC_{50} for 6-minute exposure
9,600 ppm - LC_{50} for 20-minute exposure
7,108 ppm - LC_{50} for 60-minute exposure
4,482 ppm - $BMDL_{05}$ at 60 minutes
4,100 ppm - experimental threshold for the lethality

Endpoint: the highest exposure that caused no lethality at 60 minutes (4,100 ppm where 0% mortality)

Total uncertainty factor: 30.
Interspecies = 3 – for little interspecies variability in rats compared to mice and rabbits and an LC_{50} value for mice at 2 hours is 1890 ppm, while for rats it is calculated to be 3565 ppm.
Intraspecies = 10 – default factor used because of probability differences in response and lack of human data regarding sensitive subpopulations, i.e., asthmatics.

Adjustment factor 1/3 was used to develop consistent values based upon non-lethality data

Time scaling: $C^n \times t = k$ (ten Berge et al., 1986) n = 1.9

ACUTE NON-LETHAL INHALATION TOXICITY

Species	Concentration	Exposure Time	Effect	References
Cat	200 mg/m³ (157 ppm)	30 min	Irritation threshold	Gorbachev E.M., 1957
Rabbit	130 mg/m³ (102 ppm)	40 min	Irritation threshold	
Rabbit	50 mg/m³ (39 ppm)	40 min	Disruption of conditioned reflex activity	
Rat	17,600 ppm	6 min	Corneal opacity	Air Products and Chemicals, 1992
Rat	4,100 ppm	60 min	Corneal opacity	
Mice	141 ppm	15 min	RD_{50}	Gagnaire F., 1989

AEGL-2

- **No single-exposure inhalation scenario reported effects consistent with the AEGL-2 definition**

- **Key reference:** Kinney L.A., Valentine R., Chen H.C., Everett R.M., Kennedy G.L., Jr. (1990). Inhalation Toxicology of Methylamine. Inhalation Toxicology. 2: pp. 29-39.

  Species: Male rats, 10/group

  MMA concentrations: 75, 250, and 750 ppm

  Regimen: 6 hours/day 5 days/week for 2 weeks

RESULTS

75 ppm - caused only mild irritation in mucous of the nasal turbinate area and no unusual outward signs were seen.
This "approaches" **the NOAEL**

250 ppm - were relatively well tolerated targeting the upper respiratory tract only (focal erosions and/or ulcerations of the nasal turbinate mucosa).
The lesion is **mild but not reversible.**
The NOAEL for focal and diffuse irritation in trachea and lungs

750 ppm - not well tolerated and lead to liver damage, changes in the hematopoietic system and ~ **50% death**

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
160 ppm (200 mg/m³)	92 ppm (120 mg/ m³)	64 ppm (81 mg/m³)	31 ppm (40 mg/m³)	21 ppm (27 mg/m³)

Endpoint: the NOAEL for focal and diffuse irritation in trachea and lungs (250 ppm 6 hours/day 5 days/week for 2 weeks)

Total uncertainty factor: 30.
Interspecies = 3 – for little species variability between rats and mice based upon LC_{50} values and clinical manifestations were similar among animals exposed in both these studies; this further supported the reduction from 10 to 3.
Intraspecies = 10 – default factor used because of probability differences in response and lack of human data regarding sensitive subpopulations, i.e., asthmatics.

Adjustment factor 1/3 was used to develop consistent values based upon non-lethality data

Time scaling: $C^n \times t = k$ (ten Berge et al., 1986) n = 1.9

AEGL-1

- **Key reference:** Jeevaratnam K., Sriramachari S. (1994). Comparative Toxicity of Methyl Isocyanate and its Hydrolytic Derivatives in Rats. I. Pulmonary Histopathology in the Acute Phase. – Arch. Toxicol. 69 (1): 39-44.

  Single exposure scenario with **a 30-minute** inhalation of MMA vapors at the concentration of 19μmol/L (**465 ppm**); tested species – rats of Wistar line (males).

  - ✓ During 24 hours not a single animal died;
  - ✓ No detectable clinical disorders were observed
  - ✓ The only noteworthy lesion was interstitial pneumonitis
  - ✓ No "obvious evidence" of hemorrhaging

  But:

  - ✓ Only one concentration tested;
  - ✓ Little group (n = 4);
  - ✓ Short observation period

- **Supporting study:** Kinney L.A., Valentine R., Chen H.C., Everett R.M., Kennedy G.L., Jr. (1990). Inhalation Toxicology of Methylamine. Inhalation Toxicology. 2: pp. 29-39.

  75 ppm 6 hours/day 5 days/week for 2 weeks is considered to have "approached" the NOAEL for male rats (10/group)

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)

Endpoint: the NOAEL for notable signs of clinical discomfort in rats exposed to 465 ppm for 30 minutes

Total uncertainty factor: 30.
Interspecies = 10 – due to lack of experimental data regarding manifestations of non-lethal toxicity during single exposures for different animal species.
Intraspecies = 3 – due to the little variability expected among human subpopulations, brief exposure to 20-100 ppm produced transient eye, nose, and throat irritation, while at 10 ppm the odor is faint but readily detectable (Eastman-Kodak, 1963).

Time scaling: was not conducted. Values were held constant across all time points.

EXISTENT STANDARDS AND GUIDELINES FOR MMA

Guideline	Exposure Time				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)
AEGL-2	160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (81 mg/m^3)	31 ppm (40 mg/m^3)	21 ppm (27 mg/m^3)
AEGL-3	1100 ppm (1400 mg/m^3)	590 ppm (750 mg/m^3)	410 ppm (520 mg/m^3)	200 ppm (250 mg/m^3)	140 ppm (180 mg/m^3)
ERPG-1 (AIHA)[i]			10 ppm		
ERPG-2 (AIHA)			100 ppm		
ERPG-3 (AIHA)			500 ppm		
PEL-TWA (OSHA)[ii]					10 ppm (12 mg/m^3)
IDLH (NIOSH)[iii]		100 ppm			
REL-TWA (NIOSH)[iv]					10 ppm (12 mg/m^3) [a]
TLV-TWA (ACGIH)[v]					5 ppm (6.4 mg/m^3)
TLV-STEL (ACGIH)[vi]	15 ppm (19 mg/m^3) [b]				
MAK (Germany)[i]					10 ppm (13 mg/m^3)
MAK Peak Limit (Germany)[k]	10 ml/m^3 (13 mg/m^3) [c]				
MAC (The Netherlands)[l]	15 ppm (19 mg/m^3) [a]				5 ppm (6.4 mg/m^3)

Summary of AEGL Values for Methylamine

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoints (references)
AEGL-1 (non-disabling)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	No clinical signs of intoxication at 24 hours after exposure (Jeevaratnam K. and Sriramachari S., 1994)
AEGL-2 (disabling)	160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (81 mg/m^3)	31 ppm (40 mg/m^3)	21 ppm (27 mg/m^3)	NOAEL for lung lesions (Kinney et al., 1990)
AEGL-3 (Lethal)	1100 ppm (1400 mg/m^3)	590 ppm (750 mg/m^3)	410 ppm (520 mg/m^3)	200 ppm (250 mg/m^3)	140 ppm (180 mg/m^3)	NOAEL for lethality at 1 hour (Ulrich et al., 1994).

ACUTE EXPOSURE GUIDELINE LEVELS

FOR

TRIMETHYLAMINE (CAS Reg. No. 75-50-3)

AUTHOR:
Valentin Ye. Zhukov
RIHTOP Staff Scientist

CHEMICAL MANAGER:
Iris A. Camacho
U.S. EPA

NAC/ AEGL MEETING,
Washington, DC
JUNE 13 -15, 2005

CHEMICAL AND PHYSICAL PROPERTIES

COMMON SYNONYMS:	N,N-dimethylmethylamine; n,n-dimethylmethamine; trimethylamine gas
Physical state	Gas (colorless)
Vapor Density	2.0 (air =1)
Flammability limits in air	2 – 11% (by volume)
Vapor Pressure	1610 mm Hg @ 25 °C
Boiling point	3.5 °C (1 atm)
Density	0.662 g/cm^3
Water solubility	Well soluble in water and organic solvents
Odor threshold	0.80 ppm (2.0 mg/m^3) (Rotenberg and Mashbitz, 1967; AIHA, 1993)
Conversion factors	1 ppm = 2.41 mg/m^3; 1 mg/m^3 = 0.4136 ppm

Acute Lethality for Trimethylamine

Species	Concentration (ppm)	Exposure time	Effect	References
Mice	7,790	2-hr	LC_{50}	Rotenberg, and Mashbitz (1967)
Rats	11,866	20-min	LC_{50}	Air Product (1992)
	7,913	1-hr	LC_{50}	Air Product (1992)
	3,500	4-hrs	LC_{50}	Kinney L. A. et al. (1990)
	4,394	4-hrs	LC_{50}	Koch et al. (1980)

Calculation of Benchmark Concentrations (BMC)

Air Product data (1992)

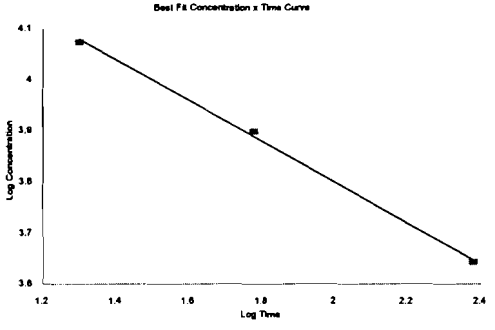
Exposure duration (min)	Actual concentration (ppm)	# dead/# total animals
20	11,200	2/10
20	12,700	6/10
20	16,200	8/10
20	14,100	9/10
20	12,700	9/10
20	18,200	10/10
60	6,150	1/10
60	7,100	3/10
60	7,720	3/10
60	7,680	4/10
60	8,170	7/10

20-minutes			
BMC_{01}	$BMCL_{01}$	BMC_{05}	$BMCL_{05}$
7,421.68	4,428.66	8,515.31	**5,718.6**

60-minutes			
BMC_{01}	$BMCL_{01}$	BMC_{05}	$BMCL_{05}$
5197.44	2742.16	5878.46	**3840.91**

Derivation of *n* for time-scaling calculations

Time (min)	Conc (ppm)	Log Time	Log Conc	Source	Regression Output:	
20	11866	1.3010	4.0743	Air Product data 1992	Intercept	4.6013
60	7913	1.7782	3.8983	Air Product data 1992	Slope	-0.4008
240	4394	2.3802	3.6429	Koch 1980	R Squared	0.9985
					Correlation	-0.9992
n = 2.49					Degrees of Freedom	1
k = 301350715592.54= 3.0 x 10^{11}ppm• min					Observations	3



Clinical pathology data in rats exposed to TMA for 6 hrs, 5 days/week for 2 weeks*

	INCIDENCE/SEVERITY PER 5 RATS EXPOSED Severity: 1, slight; 2, moderate; P, present							
	0 ppm		75 ppm TMA		250 ppm TMA		750 ppm TMA	
Finding	Day 10	Recovery day 14	Day 10	Recovery day 14	Day 10	Recovery day 14	Day 10	Recovery day 14
Nasal Cavity and turbinates (Hyperemia/congestion with edema, nasal mucosa, respiratory region)	0/0	0/0	4/P	4/P	5/P	3/P	5/P	5/P
Nasal Cavity and turbinates (epithelial degeneration/ necrosis/atrophy, nasal mucosa, respiratory region	0/0	0/0	5/1	5/1	4/1	4/1	5/2	5/1
Nasal Cavity and turbinates (Regeneration/ squamous metaplasia, focal, nasal mucosa, respiratory region)	0/0	0/0	1/P	1/P	3/P	2/P	1/P	2/P
Nasal Cavity and turbinates (Blood clots/bloody, inflammatory secretion)	0/0	0/0	2/P	3/P	0/0	2/P	4/P	3/P
Trachea (Squamous metaplasia, focal)	0/0	0/0	0/0	0/0	0/0	0/0	3/P	0/0
Trachea (Tracheitis/necrosis)	0/0	0/0	1/1	0/0	0/0	1/1	3/2	0/0
Lung (Focal interstitial pneumonitis)	1/1	3/1	1/1	4/1	0/0	1/1	3/2	0/0
Lung (Emphysematous alveoli)	0/0	0/0	0/0	0/0	1/1	0/0	4/1	0/0

* Kinney et al. (1990)

AEGL-1 Values for Trimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

No AEGL-1 values were recommended due to lack of appropriate data. Absence of AEGL-1 values does not imply that exposures below the AEGL-2 are without effect.

Derivation of AEGL-2 for Trimethylamine

Key study: Kinney L.A. et al. 1990. Inhalation toxicology of trimethylamine. Inhal. Toxicology. No. 2: 41-51.

Toxicity endpoint: NOAEL for effects in the trachea at 250 ppm observed in a rat (Crl line) study that exposed animals 5 days/week for 2 weeks to TMA. 750 ppm caused persistent squamous metaplasia and moderate tracheitis.

Total uncertainty factor (UF): 30

Interspecies UF: 3. Lethality data from mice and rats suggest that the interspecies variability is small. Rotenberg and Mashbitz (1967) conducted an inhalation study in mice and reported a 2-hr LC_{50}=7,790 ppm. An estimated 2-hr LC_{50} for rats of 5,743 ppm has been calculated with $C^n \times t=k$ using n=2.5 and $k=3.0 \times 10^{11}$ (see time-scaling discussion for more details). A 1.4-fold difference between the mouse and rat 2hr- LC_{50} values support the reduction of the interspecies UF from 10 to 3.

Intraspecies UF: 10. A default value of 10 was selected for intraspecies variability to protect sensitive populations such as asthmatics and people exhibiting polymorphic variations or genetic diseases associated with FMO3, which is the main enzyme that metabolizes TMA.

Derivation of AEGL-2 (continuation)

Adjustment factor based upon evaluation of empirical data: 1/3. A total UF of 30 would yield the following AEGL -2 values: 10-min=35 ppm, 30-min=20ppm, 1-hr=17 ppm, 4-hr=9.8 ppm and 8-hr=7.4ppm. Comparison of LC50 data for DMA and TMA using the Air Product study (1992) found that DMA is ~1.5 more toxic than TMA. The proposed AEGL-2 values using a total UF=30 are lower than those proposed for DMA. Therefore, an adjustment factor of 1/3 is proposed to obtain AEGL-2 values that are consistent with the relative toxicity of TMA and DMA.

Total Adjustment Factor (=Total UF x Adjustment factor): 10

Time-scaling: $C^n \times t = k$. To calculate *n* for trimethylamine, a regression plot of the LC_{50} values was derived from the rat LC_{50} data (20-min, 1-hr, and 4-hour LC_{50} values of 11,866, 7,913, and 4,394 ppm, respectively) from the Air Product study (1992) and Koch et al. (1980). The regression analysis resulted in an *n* value of 2.5.

AEGL-2 values for Trimethylamine

10-minute	30-minute	1-hour	4-hour	8-hour
100 ppm (240 mg/m³)	68 ppm (160 mg/m³)	51 ppm (120 mg/m³)	29 ppm (70 mg/m³)	22 ppm (53 mg/m³)

Derivation of AEGL-3 for Trimethylamine

Key study: Raw data from inhalation study conducted by IRDC for Air Products in 1992. Data obtained by personal communication with Dr. Richard Thomas.

Toxicity endpoint: 20-min $BMCL_{05}$=5,719 ppm and 60 -min $BMCL_{05}$=3,841 ppm considered an estimate of the lethality threshold for rats.

Total uncertainty factor (UF): 30

Interspecies UF: 3. Lethality data from mice and rats suggest that the interspecies variability is small. Rotenberg and Mashbitz (1967) conducted an inhalation study in mice and reported a 2-hr LC50=7,790 ppm. An estimated 2-hr LC50 for rats of 5,743 ppm has been calculated with Cn x t=k using n=2.5 and k=3.0 x 1011 (see Appendix B). A 1.4-fold difference between the mouse and rat 2hr-LC50 values support the reduction of the interspecies UF from 10 to 3.

Intraspecies UF: 10. A default value of 10 was selected for intraspecies variability to protect sensitive populations such as asthmatics and people exhibiting polymorphic variations or genetic diseases associated with FMO3, which is the main enzyme that metabolizes TMA.

Derivation of AEGL-3 (continuation)

Adjustment factor based upon evaluation of empirical data: 1/3. A total UF of 30 would yield the following AEGL-3 values: 10-min=250 ppm, 30-min=160 ppm, 1-hr=130 ppm, 4-hr=70 ppm and 8-hr=60 ppm. These AEGL-3 values are inconsistent with subchronic data that found no lethality in rats exposed to 75, 250 or 750 ppm TMA for 6 hrs, 5 days/week for 2 weeks (Kinney et al., 1990). Using an adjustment factor of 1/3 would yield less conservative AEGL-3 numbers. The AEGL-3 values derived from a total adjustment factor of 10 for TMA are 1.3-1.5-higher than those for dimethylamine (DMA). Comparison of LC50 for DMA and TMA using the Air Product study (1992) found that DMA is ~1.5 more toxic than TMA, supporting the proposed adjustment factor of 1/3.

Total Adjustment Factor (=Total UF x Adjustment factor): 10

Time-scaling: $C^n \times t = k$. To calculate n for trimethylamine, a regression plot of the LC_{50} values was derived from the rat LC_{50} data (20-min, 1-hr, and 4-hour LC_{50} values of 11,866, 7,913, and 4,394 ppm, respectively) from the Air Product study (1992) and Koch et al. (1980). The regression analysis resulted in an *n* value of *2.5.*

AEGL-3 values for Trimethylamine

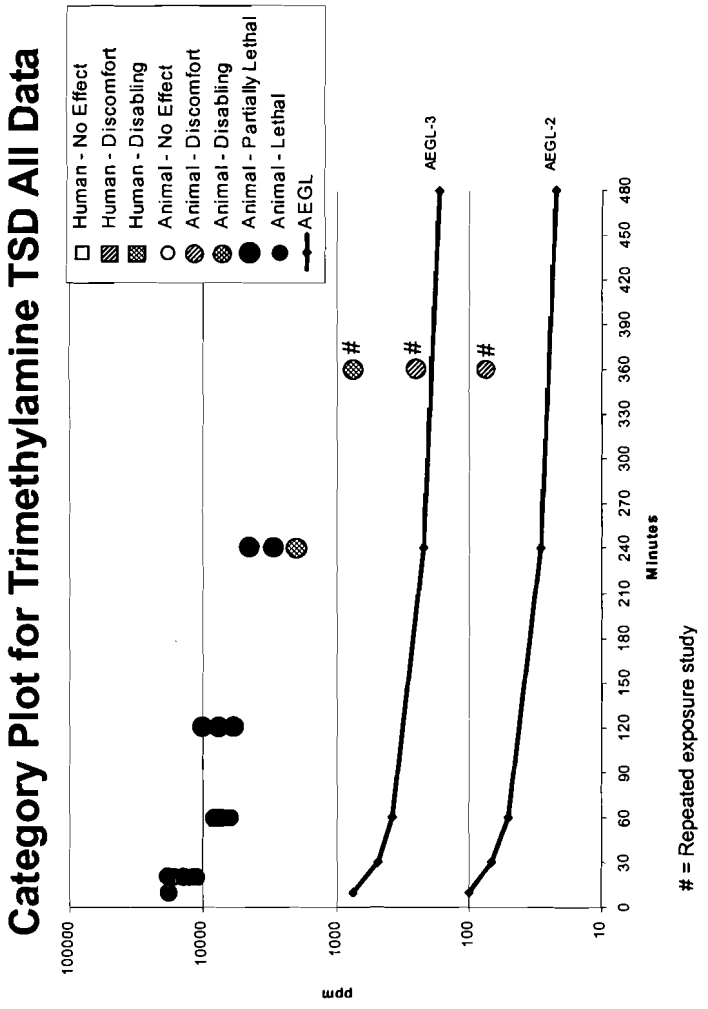
10-minute	30-minute	1-hour	4-hour	8-hour
750 ppm (1,800 mg/m³)	490 ppm (1,200 mg/m³)	380 ppm (920 mg/m³)	220 ppm (530 mg/m³)	170 ppm (410 mg/m³)

Summary of AEGL Values for Trimethylamine

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoints
AEGL -1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended
AEGL – 2 (Disabling)	100 ppm (240 mg/m³)	68 ppm (160 mg/m³)	51 ppm (120 mg/m³)	29 ppm (70 mg/m³)	22 ppm (53 mg/m³)	NOAEL for trachea toxicity in rats (Kinney et al., 1990)
AEGL – 3 (Lethal)	750 ppm (1,800 mg/m³)	490 ppm (1,200 mg/m³)	380 ppm (920 mg/m³)	220 ppm (530 mg/m³)	170 ppm (410 mg/m³)	$BMCL_{05}$ in rats (Air Product study, 1992)

Extant Standards and Guidelines for Trimethylamine

Guideline	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	100 ppm	68 ppm	51 ppm	29 ppm	22 ppm
AEGL-3	750 ppm	490 ppm	380 ppm	220 ppm	170 ppm
ERPG-1 (AIHA)			0.1 ppm		
ERPG-2 (AIHA)			100 ppm		
ERPG-3 (AIHA)			500 ppm		
STEL (AIHA)	15 ppm (15 min)				
TWA (AIHA)					5.0 ppm
MPC ind.zone.air (Russia)					2.0 ppm
MPC amb. Air					0.062 ppm
MAC-TGG					0.4 ppm
TLV (ACGIH)					5 ppm



ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYLAMINE (CAS NO. 75-04-7)

$C_2H_5NH_2$

PRESENTED by:

CHEMICAL MANAGER
MARQUEA D. KING, PH.D.
U.S. EPA

ON BEHALF of:

VALERY KIRYUKHIN
RESEARCH INSTITUTE OF HYGIENE, TOXICOLOGY AND OCCUPATIONAL PATHOLOGY
(RIHTOP), RUSSIA

NAC/AEGL MEETING, Washington, DC
JUNE 13-15, 2005

ETHYLAMINE OCCURENCE

Nature	- sea weeds; - degradation products of zoogenic organics
Industry	- synthesis of diethylamine, triethylamine, precursor simazin production, - synthesis of cosmetic and medicinal drugs; emulsifiers, and detergents - metal corrosion inhibitor
Component of tobacco smoke	

Physical and Chemical Properties of Ethylamine

PARAMETER	VALUE
Physical State	Colorless, flammable liquid or gas, depending one the ambient temperature
Odor	Pungent or ammonia like
Solubility	Miscible with water, alcohol, ether
Coefficient octanol /water partition coefficient as log Pow	- 0.27/ - 0.08 (calculated)
Vapor Pressure	121 kPa at 20°C
Vapor Density	1.55 (Air =1)
Boiling Point	16.6°C
Flash Point	17°C, closed cup
Auto-Ignition Temperature	383.9°C
Explosive Limits	3.5 to 14 vol% in air
Melting Point	-81.1°C
Calculation Factors	**1 ppm = 1.84 mg/m³; 1 mg/m³=0.54 ppm**

EXPOSURE SYMPTOMS

Exposures from inhalation contact:

- **systemic lesion** — nausea, headache, weakness, decrease of body weight
- **conjunctiva inflammation** — conjunctivitis, blepharitis, aglia, corneal edema, liquid excretas
- **respiratory tract lesion -** — apnea, rale, asphyxia, pneumonitis, pneumonia, cough, sneezing

Exposures from dermal contact

burns, dermatitis

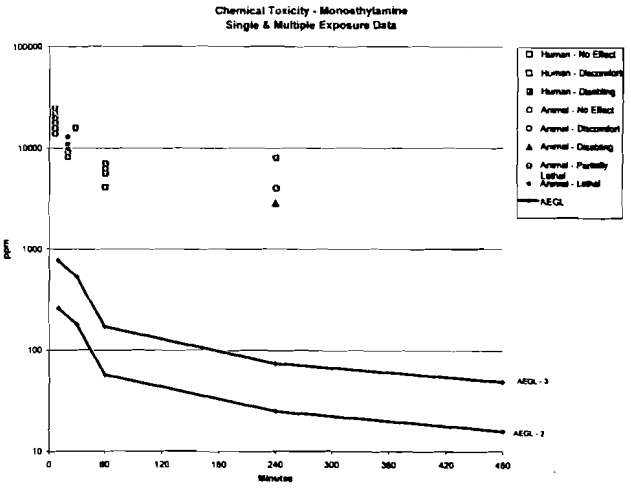
Odor Thresholds: **0.26 – 214 ppm (Ruth, J., 1986)**
97 ppm irritation

0.027 – 3.5 ppm (AIHA, 1995)

0.027 ppm (Tkachov, 1996)
0.005 ppm, non-effective

ACUTE INHALATION LETHALITY (RATS)

Concentration (ppm)	Exposure Time (min)	Effect (lethality)	References
22,200	6	LC_{50}	IRDC, 1993
9,136	20	LC_{50}	IRDC, 1993
5,540	60	LC_{50}	IRDC, 1993
16,000	28	100% lethality	MIIR, 1987
8,000	240	33.3% lethality	MIIR, 1987
4,000	240	16.7% lethality	MIIR, 1987



INHALATION TOXICITY DATA

Human studies

Tkachov et al., 1967; Tkachov, 1969:
Novokuznetsk. Industrial contamination of ambient air.
Observation: 2 years.
Children: increase in respiratory diseases rate, ears and eyes diseases.

odor threshold – 0.027 ppm
non-effective concentration
(odor absence) – 0.005 ppm

Ruth, 1986: acrid odor - 97 ppm

Clayton et al., 1981-1982:
Workers have had headache, nausea, weakness, anxiety

NIOCH (ICSK: 0153) NLM 1992:
Workers have had conjunctivitis, corneal edema, respiratory tract irritations, dermatitis, burns

Animal studies

- **Briger and Hodes, 1951:**

  Rabbits; vapor inhalation; 6 weeks × 5 days ×7 hours; 50 ppm and 100 ppm. No lethality. Eyes and lungs lesions.

- **Tkachov, 1969:**

  Vapour exposure; 93 days; 2.0 – 0.008 ppm.
  0.005 ppm is non–effect concentration

- **Research Pathology Associates, 1984:**

  Rats Fisher 344;
  250 ppm and 1,000 ppm, 10 days - necrotic inflammation of nasal cavity.
  500 ppm, 120 days – intranasal septum necrosis.

- **Bio/dynamics, Inc., 1986:**

  Vapor exposure; 2,580 ppm, 4 hours.
  Observation - 14 days. Postmortem tests.
  No lethality. Respiratory failure, keratopathy, weight loss during 1 week.

Animal studies (cont'd)

- **MIIR, 1987:**

Acute poisoning clinical observations:

- rats; inhalation exposure; concentrations 16,000 ppm; 8,000 ppm; 4,000 ppm (100% - 15% lethality);
- rabbits; percutaneous exposure (24 hours), LD_{50} = 0.53 mg/kg (71.8% solution);
- rats; intragastric exposure; LD_{50} = 390 mg/kg

- **Lynch et al., 1988:**

10 ppm and 100 ppm; 24 weeksx 5 days x 6 hours - no changes.
500 ppm; 120 days – decrease of body weight increase; nasal inflammable necrosis

- **Gagnaire et al., 1989:**

RD_{50} = 151 ppm (mice, 15 min)

- **IRDC, Air Products, 1993:**

Acute inhalation toxicity (LC_{50}) for 6, 20 and 60 min exposure. Observation – 14 days. Postmortem tests.

LC_{50}/Derivation of n

ORNL Paradigm Ethylamine, Air Products data, 1993

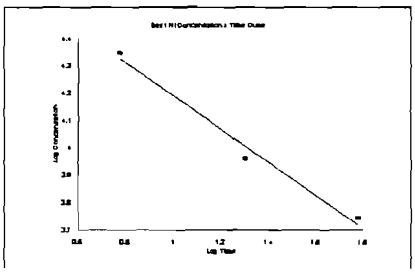
Time	Conc.	Log Time	Log Conc.
6	22200	0.7782	4.3464
20	9136	1.3010	3.9608
60	5540	1.7782	3.7435

Regression Output:	
Intercept	4.7948
Slope	-0.6050
R Squared	0.9823
Correlation	-0.9911
Degrees of Freedom	1
Observations	3

n = 1.65
k = 8.4E+07

Minutes	Conc.
30	7963.85
60	5235.91
240	2263.36
480	1488.10

Hours	Conc.
0.5	84814.25
1.0	62338.14
4.0	26947.24
8.0	17717.18



n = 1.7

AEGL-3 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
770 ppm (1400 mg/m³)	530 ppm (980 mg/m³)	170 ppm (310 mg/m³)	74 ppm (140 mg/m³)	49 ppm (90 mg/m³)

Key Studies:

International Research and Development Corp for Air Products, 1993

Test Species:

10 Sprague-Dawley rats (5 M + 5 F)

Exposure:

inhalation: 6; 20 and 60 min

Effects:

6 min. LC_{50} = 22,200 ppm
20 min. LC_{50} = 9,136 ppm
60 min. LC_{50} = 5,540 ppm

Toxicological Endpoints:

6 min. $BMCL_{05}$ = 10,457 ppm
20 min. $BMCL_{05}$ = 6,689 ppm
60 min. $BMCL_{05}$ = 1,677 ppm
estimated lethality thresholds for rats

Uncertainty Factor:

Interspecies: 3 – based upon the similarity of toxic response to ethylamine for different species, and the indicators of acute toxicity for (mice, rats and rabbits) are insignificant, varying in their LD_{50} values for oral route of administration only by 1.3 – 2.3 times

Intraspecies: 10 – a default value was used due to expected differences in response of sensitive populations to irritant gases at low exposures such as asthmatics (NRC, 2001).

Adjustment Factor:

1/3 was used to develop consistent values based upon non-lethality data. The steep dose response curve justifies an additional factor.

Time Scaling: $C^n \times t = k$ (ten Berge et al.), n = 1.7

Calculations:

$C^{1.7} \times t = k$

6 min $BMCL_{05}$ ~ 10 min
20 min $BMCL_{05}$ ~ 30 min
60 min $BMCL_{05}$ ~ 60 min, 4 and 8 hr

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
260 ppm (480 mg/m^3)	180 ppm (330 mg/m^3)	57 ppm (110 mg/m^3)	25 ppm (46 mg/m^3)	16 ppm (29 mg/m^3)

Key Studies: NRC Guidelines, 2001: Due to absence of specific data for the AEGL-2 endpoint, the use of 1/3 of AEGL-3 values has been performed.

Toxicity Endpoints: 1/3 AEGL-3 values.

Uncertainty Factors: 1/3 AEGL-3 values.

Scaling Process: 1/3 AEGL-3 values.

Time Scaling: 1/3 AEGL-3 values (n= 1.7).

AEGL-1 VALUES

Values not recommended due to insufficient data. .

SUMMARY OF PROPOSED AEGL VALUES

Summary of AEGL Values for Ethylamine

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoints (References)
AEGL-1 (no disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (disabling)	260 ppm (480 mg/m^3)	180 ppm (330 mg/m^3)	57 ppm (110 mg/m^3)	25 ppm (46 mg/m^3)	16 ppm (29 mg/m^3)	1/3 of AEGL-3 values
AEGL-3 (Lethal)	770 ppm (1400 mg/m^3)	530 ppm (980 mg/m^3)	170 ppm (310 mg/m^3)	74 ppm (140 mg/m^3)	49 ppm (90 mg/m^3)	calculated $BMCL_{05}$ for 6,20, and 60 minutes (Air Products,1993)

Existent Standards and Guidelines for Ethylamine

Guidelines	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	**260** ppm (480 mg/m^3)	**180** ppm (330 mg/m^3)	**57** ppm (110 mg/m^3)	**25** ppm (46 mg/m^3)	**16** ppm (29 mg/m^3)
AEGL-3	**770** ppm (1,400 mg/m^3)	**530** ppm (980 mg/m^3)	**170** ppm (310 mg/m^3)	**74** ppm (140 mg/m^3)	**49** ppm (90 mg/m^3)
PEL-TWA (OSHA)[c]					**10** ppm (18 mg/m^3)
REL-TWA (NIOSH)[f]					**10** ppm (18 mg/m^3)
TLV-TWA (ACGIH)[h]					**5** ppm (9.2 mg/m^3)
TLV-STEL (ACGIH)	**15** ppm (27.6 mg/m^3)				
MAK (Germany)[i]					**5** ppm (9.4 mg/m^3)

ATTACHMENT 20

BIS-CHLOROMETHYL ETHER (BCME)

$ClH_2C–O–CH_2Cl$

Draft 1

ORNL Staff Scientist: Sylvia Milanez

Chemical Manager: Ernest Falke

Chemical Reviewers: Thomas Hornshaw, Robert Benson

BCME BACKGROUND INFORMATION

★ BCME is a man-made chemical used industrially as a chloromethylating agent in the manufacture of ion-exchange resins, bactericides, pesticides, etc.

★ BCME hydrolyzes in water to HCl and formaldehyde. It is believed to exist in water in equilibrium with its hydrolysis products, with about 20% of the original compound left

★ BCME half-life in water is ~ 10-60 seconds and in humid air (81%) is ~ 7-25 hours at 20°C

★ In 1973, BCME was listed by OSHA as a human carcinogen and its use limited to controlled areas. BCME is classified as a human carcinogen by the U.S. EPA, ACGIH, IARC, and NIOSH.

★ As of 1982, BCME is not produced as a commercial product in the U.S., but small amounts may be produced or repackaged (5 U.S. suppliers in 2005).

★ A potential source of BCME exposure is spontaneous formation from the commonly used chemicals HCl and formaldehyde: mixtures of 500-5000 ppm each compound produced <0.5-179 ppb BCME (~0.01-0.001% yield).

BCME HEALTH EFFECTS

★ BCME has a "suffocating" and irritating odor. An odor detection threshold has not been reported. BCME has poor warning properties: it was "distinctly irritating" at 3 ppm, but caused severe eye damage after exposure to lower (unspecified) concentrations.

★ BCME vapor is a severe respiratory, eye, nose, and skin irritant. In humans, it has caused pulmonary edema and congestion, corneal necrosis, dyspnea, and lung cancer (shorter latency period and histology distinct from smoking-induced tumors).

★ BCME may be an alkylating agent. Conflicting results were reported regarding its ability to bind DNA.

★ BCME was positive in some, but not other, genotoxicity assays. It is unclear whether it is a genotoxic or non-genotoxic carcinogen.

★ Leong et al. (1981) suggested that there is a threshold for BCME carcinogenicity. Rats and mice had no effects from exposure to 1 or 10 ppb BCME for 6 months, but 100 ppb caused extensive toxicity and carcinogenicity (lifetime observation).

★ Occupational study of Langner (1977) also suggests there is a carcinogenicity threshold: no effects from ~3 ppm, 27 years operation

★ No information was found regarding BCME metabolism, or the metabolism of its hydrolysis products.

AEGL-1

AEGL-1 values were not recommended because effects exceeding the severity of AEGL-1 occurred at concentrations that did not produce sensory irritation in humans or animals.

AEGL-2

Key study: Drew et al. 1975. Lifetime observation after a single 7-hour exposure to 0.7, 2.1, 6.9, or 9.5 ppm BCME in rats and 0.7, 2.1, 5.6, or 9.9 ppm BCME in hamsters (25/conc). At 0.7 ppm, both species had inc lung-to-BW ratios, and saw inc in tracheal epithelial hyperplasia in rats, and pneumonitis in hamsters. At ≥2.1 ppm, both species had mortality and lung lesions. An adjustment factor of 3 was applied to LOAEL of 0.7 ppm to estimate a NOAEL of 0.23 ppm = POD

Toxicity endpoint: 0.23 ppm as NOAEL for irreversible respiratory lesions in rats and hamsters

Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive *n* empirically, so used default n=3 and n=1 to extrapolate to <7 hours and >7 hours, respectively, except adopted 30-minute values for 10 minutes

Total uncertainty factor: 10

Interspecies: 3 - BCME caused a similar toxic response in two species at the same test concentration in the key study, and is expected to cause toxicity similarly in human lungs, which are the target organ

Intraspecies: 3 - Respiratory tract tissue damage from a proximally-acting irritant gas with a steep dose-response is not likely to vary greatly among humans. Using default UF of 10 would bring the 4-hour and 8-hour values below 0.010 ppm, which was shown to be a no-effect level after 129 exposures in rats and mice (6 hours/day, 5 days/week; Leong et al. 1981).

AEGL-2				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm

AEGL-3

Key study: Drew et al. 1975. Rats and hamsters (50/species/conc) were subjected to 1, 3, 10, or 30 six-hour exposures to 1 ppm BCME and lifetime observation. AEGL-3 values were based on the single-exposure scenario, which resulted in slightly inc incidences of lung lesions in rats and hamsters, whereas 3 exposures caused lung lesions and increased mortality.

Toxicity endpoint: NOEL for lethality from lung lesions

Scaling: as for AEGL-2

Total uncertainty factor: 10

Interspecies: 3: NOEL for lethality was the same in two species in the key study, and lethality is expected to occur by a similar mode in humans as in animals

Intraspecies: 3: NOEL for lethality from respiratory tract lesions caused by a proximally-acting, irritant gas with a steep dose-response is not likely to vary greatly among humans.

AEGL-3				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

CHLOROMETHYL METHYL ETHER, TECHNICAL GRADE

$H_3C–O–CH_2Cl$

ATTACHMENT 21

Draft 1: March, 1998
Draft 2: October, 2000 (change n default, add 10' values)
Interim 1: NAS/COT January 2004

SUMMARY OF MAJOR CHANGES SUGGESTED BY COT:

1. USE SINGLE-EXPOSURE STUDY FOR AEGL-2 DERIVATION, INSTEAD OF MULTIPLE-EXPOSURE STUDY

2. CLARIFY / STRENGTHEN UNCERTAINTY FACTOR RATIONALES

3. PROVIDE MORE DETAIL ON CARCINOGEN RISK ASSESSMENT AND ITS IMPACT ON AEGL VALUES

BACKGROUND INFORMATION

★ CMME is a highly volatile, colorless, flammable liquid with an irritating odor barely detectable at 1.5 ppm and easily detectable at 23 ppm.

★ CMME vapor is a severe respiratory, eye, nose, and skin irritant, and high concs. can lead to delayed fatal pulmonary edema and respiratory cancer.

★ People are only exposed to technical grade CMME, which contains ~ 1-10% bis- chloromethyl ether (BCME). BCME is ~ 10-fold more toxic and carcinogenic than CMME.

★ CMME decomposes rapidly and irreversibly in water ($t_{½}$ est. as <1 sec) or humid air ($t_{½}$ 2.3 min-6.5 hrs) to form methanol, formaldehyde and HCl. The latter two can recombine reversibly to form BCME to an unknown extent.

AEGL-1

AEGL-1 values were not derived because no studies were available in which toxicity was limited to AEGL-1 effects.

AEGL-2

Key study: Drew et al. 1975. Acute toxicity study in which rats and hamsters were exposed to 12.5-225 ppm CMME (BCME content ??) for 7 hours and observed for 14 days. A dose-related increase in lung congestion, edema, hemorrhage occurred. The LOAEL of 12.5 ppm was divided by 3 to estimate a NOAEL of 4.2 ppm for serious or irreversible lung lesions in both species. The number of animals/group was not given but appeared to be >10.

Toxicity endpoint: NOAEL for serious or irreversible lung lesions in rats and hamsters.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); used default n=3 and n=1 and adopted 30-minute values for 10 minutes.

Total uncertainty factor: 10

Interspecies: 3 - CMME is a locally-acting respiratory tract irritant gas that caused a similar degree of lung toxicity in two animal species, and is expected to cause similar toxicity in human lungs, which are the target organ

Intraspecies: 3 - respiratory tract tissue damage from an irritant gas that acts proximally is not likely to vary greatly among humans.

Modifying factor: 3: because the content of BCME (which is more toxic than CMME) in technical grade CMME in the key study was unknown, and 3 is the geometric mean of the typical range of 1-10% BCME contamination

AEGL-2				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.34 ppm	0.34 ppm	0.27 ppm	0.17 ppm	0.12 ppm

AEGL-3

Key study: Drew et al. 1975, as for AEGL-2 derivation. Rat 7-hour exposure inhalation LC_{50} study I which rats were exposed to 12.5-225 ppm CMME for 7 hours and observed for 14 days. Assuming n = 20 for all dose groups, a $BMCL_{05}$ of 18 ppm was calculated for hamsters and 19 ppm for rats using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2.; the lower value was used for AEGL-3 derivation.

Toxicity endpoint: NOEL for lethality (from extreme lung irritation), based on the calculated lethality $BMCL_{05}$ of 18 ppm for hamsters.

Scaling: as for AEGL-2

Total uncertainty factor: 10

Interspecies: 3 - the NOEL for lethality was virtually the same in two species in the key study, and lethality is expected to occur by a similar mode in humans and animals

Intraspecies: 3 - the NOEL for lethality from severe lung lesions caused by a proximally-acting, irritant gas is not likely to vary greatly among humans. CMME.

Modifying factor: 3: because the content of BCME (which is more toxic than CMME) in technical grade CMME in the key study was unknown, and 3 is the geometric mean of the typical range of 1-10% BCME contamination

AEGL-3				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1.4 ppm	1.4 ppm	1.1 ppm	0.72 ppm	0.53 ppm

Summary of AEGL Values for CMME					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	Not Recommended (No studies were available in which toxicity was limited to AEGL-1 effects)				
AEGL-2	0.34 ppm	0.34 ppm	0.27 ppm	0.17 ppm	0.12 ppm
AEGL-3	1.4 ppm	1.4 ppm	1.1 ppm	0.72 ppm	0.53 ppm

COMPARISON OF CMME AND BCME AEGL VALUES

BCME					
Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	NR				
AEGL-2	0.055 ppm	0.055 ppm	0.044 ppm	0.028 ppm	0.020 ppm
AEGL-3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm

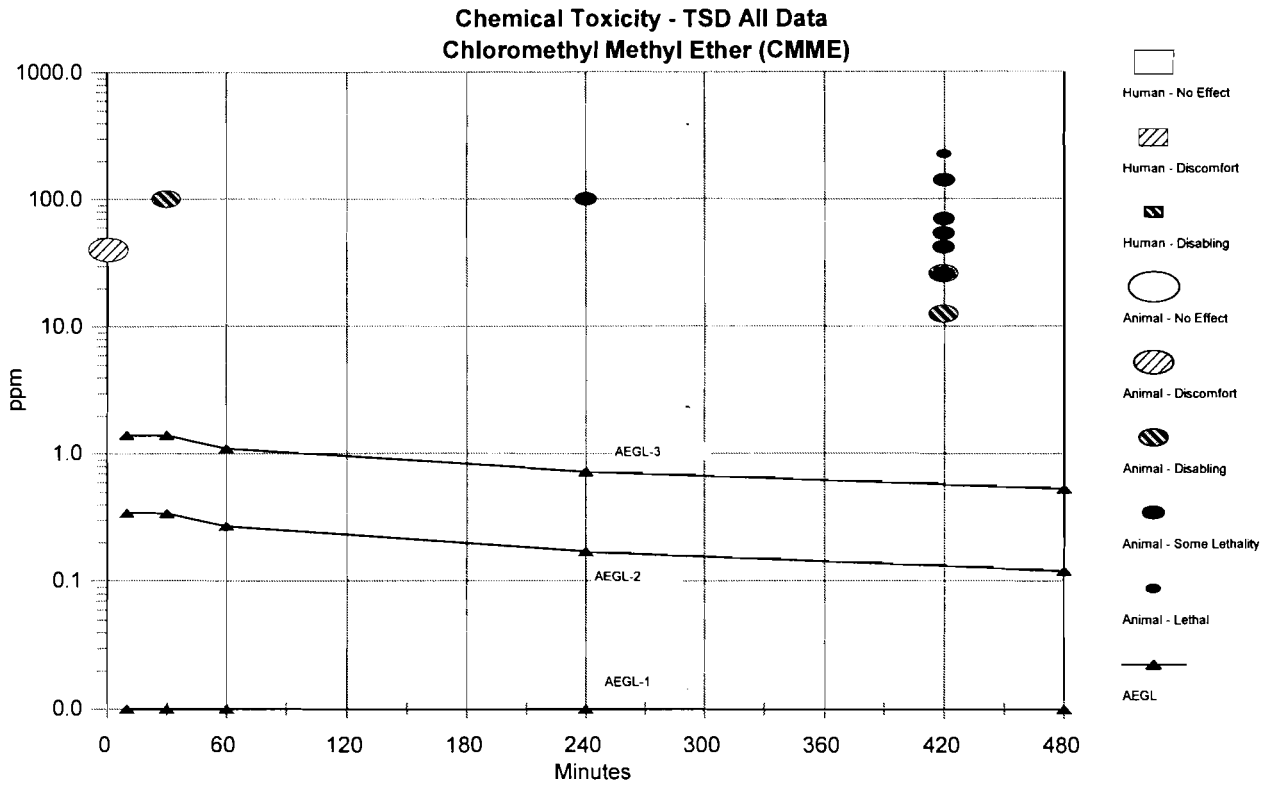
CMME (AEGL-2 POD= 4.2 ppm for 7 hrs)					
Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	NR				
AEGL-2	0.34 ppm	0.34 ppm	0.27 ppm	0.17 ppm	0.12 ppm
AEGL-3	1.4 ppm	1.4 ppm	1.1 ppm	0.72 ppm	0.53 ppm

AEGL-2: 6x BCME values (4.5x previous CMME values)

<u>PREVIOUS</u> interim/proposed CMME (AEGL-2 POD= 1 ppm for 6 hrs)					
Level	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	NR				
AEGL-2	0.076 ppm	0.076 ppm	0.061 ppm	0.038 ppm	0.025 ppm
AEGL-3	1.2 ppm	1.2 ppm	0.94 ppm	0.59 ppm	0.43 ppm

AEGL-2: 1.4x BCME values

Category Plot for Chloromethyl Methyl Ether



Note: Multiple-exposure studies were not included

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

April 12-14, 2005

Final Meeting-36 Highlights

U.S. EPA, Office of Research and Development
Building C, Auditorium
109 T.W. Alexander Drive
Research Triangle Park, NC 27709

INTRODUCTION

Chairman George Rusch welcomed the committee and thanked George Woodall for the meeting arrangements. Dr. Tim Oppelt, Acting Director of the U.S. EPA Office of Research and development, welcomed the group to Research Triangle Park

George Rusch informed the committee that Dr. Doan Hansen, former Department of Energy representative to the NAC/AEGL, had died from a heart attack on March 12, 2005.

The draft NAC/AEGL-35 meeting highlights were reviewed. John Morawetz provided several comments, especially with regard to human data descriptions and including more detail documenting the history of AEGL definition issues. Marc Ruijten suggested editorial corrections These suggestions were incorporated into the highlights. A motion was made by Marc Ruijten and seconded by Richard Thomas to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-35 meeting highlights is attached (Appendix B).

The highlights of the NAC/AEGL-36 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-36 Agenda.

REVIEW OF NAS/COT-15 (February, 2005) MEETING

Ernest Falke and George Rusch reviewed process/procedure issues discussed at NAS/COT-15; resolution of these issues is designed to improve productivity (rate of publication). Currently, the NAS/COT subcommittee has published 24 "final" AEGL TSDs. The NAC has completed 139 chemicals. Dr. Don Gardner, the new NAS/ COT subcommittee chair, has a goal of finalizing 20 chemicals each year. In order to accomplish this goal, the following items were suggested (1)

limit all chemicals to three COT reviewers; (2) limit each TSD to two visits to COT; (3) improve dialog/come to closure at the meeting (reviewers can't push open-ended issues); (4) resolve conflicting reviewer comments prior to publication of the interim report; (5) shorten the TSD length (delete non-essential references/study descriptions); and (6) clarify the application of uncertainty factors (UFs) and modifying factors (MFs) (see below).

Iris Camacho then discussed issues relating to the NAC/AEGL Standing Operating Procedures (SOPs) (Attachment 3). Among the SOP issues discussed at NAS/COT-15 were rounding of the time scaling exponent 'n' and use of UFs and MFs.

The NAS/COT agreed that, where data allow, round empirically-derived values of the exponent 'n' to two significant figures. After a short discussion, a motion was made by John Hinz and seconded by George Woodall to adopt this suggested approach for derivation of the time scaling exponent. The motion passed unanimously by a show of hands (Appendix C).

The NAS/COT subcommittee expressed concerns on the current approach used to justify/adjust UFs downward from the default value of 10, because often it is not possible to assign the adjustment between inter- and intraspecies variability. The NAS/COT suggested applying the default UFs unless there are data showing that interspecies or intraspecies differences merit a reduction (adhere strictly to SOP in these cases). Then, if the overall data base suggests that values are too low, apply an alternate factor (e.g. MF) for adjusting the AEGL values to be consistent with the human and/or animal supporting data. Another approach recommended to the NAC/AEGL by Iris Camacho was to create the weight-of-evidence factor (WOEF). This approach would not change the AEGL values, but the derivation would be more transparent and consistent. The magnitude of the weight-of-evidence factor would be >0. Values less than 1 should be expressed as a fraction such as 1/3 or 1/10, to be consistent with the UF progression of 1, 3, and 10, and to avoid a repeating decimal. The rationale for the weight-of-evidence factor should include citations and explanations of the supporting human and/or animal data; and justification for the selected factor, including discussion of why the initially-derived AEGL values conflict with published data.

Thorough discussion centered around an acceptable name for the alternate factor, modifying the definition of UFs and modifying the definition of MFs. Ursula Gundert-Remy agreed with the proposal for the WOEF, but recommended being cautious about using the expression "data-derived UF". In addition, she asked how this new factor would consider kinetic/dynamic differences. Bob Benson also agreed with using a WOEF, because it is makes the derivations more transparent. Tom Hornshaw asked whether there was a precedence within EPA for use of a WOEF. Bob Benson indicated that the EPA's IRIS program has a provision to allow a modifying factor < 1. Jonathan Borak found the term WOEF confusing and felt it would conflict with the cancer terminology; he supported the concept of an adjustment factor. Kowetha Davidson mentioned that there are provisions in EPA's RfD guidelines to allow MF <1. Marc Ruijten suggested revisiting the UF definitions in the SOP so UFs<1 are allowed. Richard Thomas favored revising the MF definition to allow a MF<1; he did not like the term WOEF. Marc Ruijten said that the WOEF would confirm the reasonableness of the values; he supports the

WOEF if restricted to such purpose. Ursula Gundery-Remy recommended separating the MF from WOEF.

George Rusch then suggested analyzing UF rationales of final and interim TSDs where UFs<10 were utilized in order to be consistent with supporting data. He favored a data-adjustment factor applied to the total UF value because it would allow more flexibility to use an UF of 3 or 1. Analysis of UF rationales of final and interim documents will show where the NAC has deviated from the SOP thus far, and may provide information helpful in revising/expanding the UF definitions/applications in the SOP. The chemical managers were tasked to evaluate the UF justifications in their chemicals and to provide this information to Iris Camacho or Ernest Falke before the June, 2005, meeting. The UF application sections of the SOP could then be revised where appropriate, and this approach will be presented to the NAS/COT subcommittee. Marc Ruijten supported George Rusch's suggestion because SOP definitions are too restricted. In addition, he suggested eliminating the two SOP sections that deal with adjusting the inter- and the intraspecies UF in order to be consistent with the empirical data, redefining the inter- and intraspecies UFs. George Woodall stated that EPA has an uncertainty factor data base in preparation; he will provide Iris Camacho with appropriate information from this data base.

The key points of this discussion are as follows: (1) do not expand the MF definition; (2) analyze UF usage and then revise the SOP; (3) create a 4th factor that takes into consideration professional judgement/weight-of-evidence. (All NAC members raised their hands when asked if they favored the creation of such a factor).

SOP PBPK White Paper

Jim Dennison presented information concerning the use of PBPK modeling in AEGL value development ("The White Paper") (Attachment 4). After approval by the NAC and COT AEGL subcommittee, this guidance may become part of the revised SOP. Major discussion points included application of the UF before or after the dose metric and choice of workload parameters. The following guests from EPA, RTP were present for the discussion: Marina Evans, Will Boyes, Paul Schlosser, Jane-Ellen Simmons, and Vernon Benignus. Will Boyes advocated applying the UF at the end of the PBPK analysis, and suggested that chemical assessment should be separated from policy. Vernon Benignus stated that if a PK model was validated in both humans and an animal species, the UF would equal 1, and that applying a dose adjustment factor at step 4 in the model creates a policy decision. Paul Schlosser stated that if it is assumed that humans and animals respond at the same target concentration, then the interspecies UF should be applied at the end of the PBPK analysis. Jane Ellen Simmons suggested looking at blood concentrations in multiple species where data are available. Ursula Gundery-Remy said that more discussion on the dynamic component in the white paper is needed to avoid the idea that the kinetic information is predicting the dynamic component. Ursula stated that the ACUTEX program does not consider sensitive populations in the analysis. George Rusch asked the committee whether they favored applying the UF at an intermediate step or at the end of the calculations. There was more general support for UF application in the middle of the assessment. Marc Ruijten suggested including the

workload information in an appendix (as is done for carcinogenicity) and not to consider workload for derivations.

Time will be set aside at the June meeting to compare examples of AEGL values derived by PBPK modeling and the traditional approach utilizing a key study and endpoint and time scaling. These examples will include examples with and without workload.

CHEMICAL PRIORITY LIST

Marquea King discussed the revised AEGL chemical priority list (Attachment 5). Current sources and strategies for identifying priority AEGL chemicals were reviewed. Also discussed was the fact that the SOP contains provisions for modifying the chemical priority list. NAC members suggested the following additional sources for identifying potential priority chemicals: FBI, NOA-CAMEO, and HPV/OECD. George Rusch suggested that the DOE TEELs be provided, rather than IDLH values, on the chemical list. After this discussion, Marquea King requested that NAC members provide her with any additional feedback on the chemical priority list within one month.

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

Comments from the *Federal Register Notice* of September 7, 2004, on the proposed AEGL values for epichlorohydrin and acetone were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

Epichlorohydrin (CAS No. 106-89-8)

Chemical Manager: Richard Thomas, INTERCET, Ltd.
Staff Scientist: Kowetha Davidson, ORNL

Comments from the *Federal Register Notice* on the proposed AEGL values for epichlorohydrin were reviewed and discussed by Kowetha Davidson (Attachment 6). Comments were received from Ernest Falke who commented that the odor threshold should not be used as support for AEGL-1 and that secondary sources should not be used for derivation of AEGL values. Two options were presented. Proposal No. 1 was to use the UCC (1983) report showing pharyngeal irritation in one of four subjects exposed to 68 ppm epichlorohydrin for 2 minutes. Exposure to 136 ppm resulted in ocular and pharyngeal irritation in two of the four subjects. Application of an intraspecies UF of 3 to the POD of 68 ppm and time scaling using n= 0.87, would result in a 10-min AEGL-1 value of 3.6 ppm. This value would be adopted for all time points (mild irritation). Proposal No. 2 was to not recommend AEGL-1 values. After discussion, a motion was made by Marc Ruijten and seconded by George Woodall to base AEGL-1 values on a NOEL for irritation in humans exposed to 17 ppm epichlorohydrin for 2 minutes (UCC, 1983). An uncertainty factor

of 3 was applied, and the resulting value of 5.7 ppm would be adopted at all time points (mild irritation). The motion carried (YES:16; NO: 0; ABSTAIN: 0) (Appendix D). John Morawetz and Kowetha Davidson will work together to revise descriptions of human studies.

Summary of Interim AEGL-1 Values for Epichlorohydrin						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	5.7 ppm	5.7 ppm	5.7 ppm	5.7 ppm	5.7 ppm	NOAEL for irritation in humans (UCC, 1983)

Acetone (CAS No. 67-64-2)

Staff Scientist: Jens-Uwe Voss
Chemical Manager: Nancy Kim, State of New York

Comments from the *Federal Register Notice* on the proposed AEGL values for acetone were reviewed and discussed by Ursula Gundert-Remy (Attachment 7). Comments were received from the Global Acetate Manufacturers Association (GAMA) and John Morawetz (ICUWC). Gama commented on all three AEGL tiers. Comments on AEGL-2 and AEGL-3 values suggested using human case report data and PBPK modeling rather than using animal data. AEGL-1 comments from GAMA included the selection of an "outdated" key study, non-conformance with the SOP regarding sensory irritation (acetone is a mild sensory irritant and proposed AEGL-1 values are too low), and the AEGL-1 values and LOA very close to one another. Mr. Morawetz was concerned with the POD selected for AEGL-1; he felt that the POD was a threshold, not a NOAEL for irritation, and thus an additional modifying factor may be appropriate. Also, of the 4 studies used for AEGL-1, Mr. Morawetz felt that the Nelson (1943) study was not appropriate because of only nominal exposure/methodology issues. Also, this study was not considered appropriate for derivation of AEGL values for acetylaldehyde. After much discussion, a motion was made by Bob Benson and seconded by George Rodgers to raise the proposed AEGL values for acetone to interim status. The motion carried (YES: 15; NO: 0; ABSTAIN: 0) (Appendix E). The Nelson study will be removed as support for AEGL-1.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS ON THE INTERIM AEGL VALUES

Allyl Alcohol (CAS No. 107-18-6)

Staff Scientist: Claudia M. Troxel, CMTox, Inc.
Chemical Manager: Nancy Kim, State of New York

Claudia Troxel discussed the data set and COT/AEGL's comments (Attachment 8). The COT/AEGL had two main areas of concern: (1) selection of an interspecies UF of 1 in the derivation of AEGL-3 values; and (2) rounding of the experimentally-derived value of n = 0.8 to n = 1 is not consistent with the SOP. Susan Ripple informed the committee that Dow Chemical has unpublished data that may impact the derivation of AEGL values for allyl alcohol. Thus, this chemical was deferred to a future NAC meting so that the Dow data may be evaluated and included in the TSD if appropriate.

Iron Pentacarbonyl (CAS No. 13463-40-6)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Ernest Falke, U.S. EPA

Bob Young discussed the data set and COT/AEGL's comments (Attachment 9). The COT/AEGL had one main area of concern: the derived value of n = 1 for time scaling AEGL-3 values. This value of n = 1 was developed based upon the similarity of Ct products using one 30-minute rat LC_{50} value and one 4-hour rat LC_{50} value. Due to a paucity of data, the COT suggested using the default time scaling values of n = 1 or n = 3. Using this approach, proposed AEGL-3 values were 0.33 ppm, 0.23 ppm, 0.18 ppm, 0.11 ppm, and 0.075 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. These revised values are more protective than the originally proposed values but are justified by the SOP. The AEGL-2 values (1/3 of AEGL-3 values) are also adjusted accordingly. After discussion, a motion was made by Richard Thomas and seconded by Ernest Falke to adopt AEGL-3 values as proposed, except that the 30-minute value should be adopted as the 10-minute value because the POD was 4-hours. The motion carried (YES: 16; NO: 1; ABSTAIN: 1) (APPENDIX F).

Summary of AEGL Values for Iron Pentacarbonyl

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not Recommended
AEGL–2	0.077 ppm	0.077 ppm	0.060 ppm	0.037 ppm	0.025 ppm	⅓ the AEGL-3 values
AEGL–3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm	$BMCL_{05}$ for death in rats (BASF, 1995)

Ammonia (CAS No. 7664-41-7)

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

Kowetha Davidson discussed the data set and COT/AEGL's comments (Attachment 10). Mr. William Herz, Director of Scientific Programs, The Fertilizer Institute was present for the

discussion. The COT/AEGL had five main areas of concern: (1) selection of intraspecies UFs for AEGL-1, AEGL-2, and AEGL-3; (2) Interspecies UF for AEGL-3; (3) derivation of 5-minute AEGL values; (4) revision of the summary of the Verberk (1977) study; and (5) Selection of the POD for AEGL-2. After discussion, the NAC decided to retain current uncertainty factors but to strengthen/clarify the justifications. NAC members should send any suggestions for strengthening these justifications to Dr. Davidson for inclusion in the TSD, and she will send the response to George Rusch, Ernest Falke, and Susan Ripple for review. The NAC also decided not to include 5-minute AEGL values and to revise the description of the Verberk study by expanding the experiment table in the TSD. After more discussion regarding derivation of AEGL-2 values, a motion was made by Steve Barbee and seconded by Richard Thomas to adopt AEGL-2 values of 220 ppm, 220 ppm, 160 ppm, 110 ppm, and 110 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. These values are based on irritation in humans exposed to 110 ppm for 2 hours (Verberk, 1977). An intraspecies UF of 1 was applied because unbearable irritation was not observed in this study until the concentration reached 140 ppm. Time scaling was accomplished utilizing n = 2 derived from mouse and rat lethality data. The 4-hour value was adopted as the 8-hour value because the maximum severity rating for irritation (Verberk, 1977) changed very little between 1 and 2 hours and thus is not expected to change from 4- to 8-hours. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a 10-min value (380 ppm) that might impair escape. Values are supported by data of Cole et al. (1977) and Silverman et al. (1949) showing no serious irreversible effects at 336 ppm or 500 ppm, respectively. The motion carried (YES: 10; NO: 4; ABSTAIN: 3) (APPENDIX G).

Summary of AEGL-2 Values for Ammonia						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–2	220 ppm	220 ppm	160 ppm	110 ppm	110 ppm	NOAEL for irritation in humans (Verberk, 1977)

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

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

Ursula Gundert-Remy discussed the data set and COT/AEGL's comments (Attachment 11). The COT/AEGL had three main areas of concern: (1) suitability of the Renshaw data for basis of AEGL-1; (2) time scaling exponent, n, was derived from lethality data from an aerosol exposure (AEGL-2 values); and (3) AEGL-3 values should be based on vapor, not aerosol, data. After discussion, the NAC decided to resubmit the Renshaw data to the COT and support the AEGL-1 POD with the Lomax et al. (1994) study showing that 5 ppm, 6 hours/day for 2 weeks was a NOEL for histopathology in mice. AEGL-3 values will remain based on the aerosol data, but the

BASF (1980) vapor data will be used as support (show of hands). A motion was then made by Marc Ruijten and seconded by Ernest Falke to retain and again present the current AEGL-2 values (68 ppm, 68 ppm, 46 ppm, 21 ppm, and 14 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) to the COT and to give the staff scientist the authority to provide AEGL-2 values utilizing the default exponent of n = 1 or n = 3 (66 ppm, 45 ppm, 36 ppm, 19 ppm, and 9.4 ppm) for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively as an acceptable set of alternate AEGL-2 values if the COT continues to reject the originally-derived values. The two sets of values are similar to one another. The motion carried (YES: 16; NO: 0; ABSTAIN: 0) (APPENDIX H).

REVIEW of PRIORITY CHEMICALS

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

Staff Scientist: Dana Glass, ORNL
Chemical Manager: Steve Barbee, Arch Chemical

Dana Glass reviewed the available data for methyl t-butyl ether (MTBE) (Attachment12). Proposed AEGL-1 values (50 ppm at all time points) were based on the highest NOEL reported in humans (50 ppm for 2 hours; Nihlen et al., 1998). No UF was applied because the POD was a NOEL in humans. Values were held constant across all time periods. Proposed AEGL-2 values (1400 ppm, 1400 ppm, 980 ppm, 400 ppm, and 400 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on transient central nervous system effects in rats exposed to 4000 ppm for 6 hours (Daughtrey et al., 1997). An interspecies UF of 3 was proposed because PBPK modeling data suggest that humans have a 1.5 to 2.5-fold increase of MTBE concentration in blood compared to rats. An intraspecies UF of 3 was also proposed because variability of CNS depression is no greater than 3-fold in the human population. Time scaling was accomplished using an exponent of n = 2, based on rat and mouse lethality data. The 4-hour value was proposed as the 8-hour value because steady state is achieved by 2 hours in the rat and 4 hours in humans. The 30-min value was proposed as the 10-min value because the POD was >4 hours. Proposed AEGL-3 values (7500 ppm, 7500 ppm, 5300 ppm, 2700 ppm, and 1900 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a 4-hour rat $BMCL_{05}$ (ARCO, 1978) Inter- and intraspecies UFs of 3 each were applied as for AEGL-2. Time scaling was accomplished with n = 2, as for proposed AEGL-2 values. It was noted that PBPK data were not sufficient for derivation of AEGL values, but blood partition data could be used to justify UFs. After discussion, a motion was made by Richard Niemier and seconded by Marc Ruijten to adopt AEGL-1 values as proposed and to support the intraspecies UF of 1 with rat data showing no effects at 400 ppm and only minor effects at 4000 ppm for 6 hours. The motion carried (YES: 17; NO: 0; ABSTAIN: 0) (APPENDIX I).

A motion was then made by Richard Niemier and seconded by John Hinz to adopt AEGL-2 values of 1400 ppm, 800 ppm, 570 ppm, 400 ppm, and 400 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on a POD of 4000 ppm for 2 hours. This POD is derived from the transient central nervous system effects in rats exposed to 4000 ppm for 6 hours (Daughtrey et al., 1997). However, because data show that steady state is achieved in 2 hours in the rat, the

two hour time point was assumed valid for the point of departure. Time scaling was achieved using n = 2 for the 10-min, 30-min, 1- hr and 4-hr time points. The 4-hour value was adopted as the 8-hour value because steady-state is achieved in the human within 4 hours. The motion carried (YES: 15; NO: 1; ABSTAIN: 1) (APPENDIX I).

Marc Ruijten then contacted Dr. ten Berge and obtained the raw rat and mouse lethality data used to derive the n = 2 value. These data supported the ARCO (1978) data proposed as the basis of AEGL-3 values and also support the interspecies UF of 3 because the rat and mouse data are similar. A motion was then made by Marc Ruijten and seconded by George Rodgers to accept the AEGL-3 values as proposed except that the 10-minute AEGL-3 value will be time scaled because the n value was derived from data ranging from 3 minutes to 4 hours. This 10-min AEGL-3 value (13,000 ppm will be listed as a footnote because it is ≥10% of the LEL. The motion carried (YES: 14; NO: 0; ABSTAIN: 0) (APPENDIX I).

Summary of AEGL Values for Methyl t-Butyl Ether

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	50 ppm	50 ppm	50 ppm	50 ppm	50 ppm	NOEL in humans (Nihlen et al., 1998)
AEGL–2	1400 ppm	800 ppm	570 ppm	400 ppm	400 ppm	Transient CNS effects in rats (Daughtrey et al., 1997)
AEGL–3	¶13,000 ppm	7500 ppm	5300 ppm	2700 ppm	1900 ppm	$BMCL_{05}$ for death in rats (ARCO, 1978)

¶The value is higher than 10% of the lower explosive limit of MTBE in air . Therefore, safety considerations against the hazard of explosion must be taken into account.

Hexafluoroacetone (CAS No. 684-16-2)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Bob Young reviewed the available data for hexafluoroacetone (HFA) (Attachment13). AEGL-1 values were not recommended because of insufficient data. Proposed AEGL-2 values (0.076 ppm, 0.076 ppm, 0.061 ppm, 0.038 ppm, and 0.025 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a NOAEL of 1.0 ppm (6 hrs/day on gestation days 7-16) for developmental toxicity in rats (du Pont, 1989). The higher tested dose (6.9 ppm) resulted in a significantly increased incidence of malformations, an increase in total resorptions/litter, a decrease in the number of liver fetuses/litter, and decreased fetal weight. It was assumed that the effects could be induced by a single 6-hr exposure. An interspecies UF of 10 was proposed because there were data from only one animal species. An intraspecies UF of 3 was proposed because HFA does not appear to undergo significant metabolism and because the fetus is

considered a uniquely sensitive target. Time scaling was accomplished using the default values of n =1 or n =3. The 30-min value was proposed as the 10-min value because the POD was 6-hours. Proposed AEGL-3 values (19 ppm, 13 ppm, 11 ppm, 6.7 ppm, and 3.3 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a NOAEL for lethality in rats (200 ppm for 4 hours) (duPont, 1962). An interspecies UF of 10 was proposed because there were data from only one animal species. An intraspecies UF of 3 was proposed because HFA does not appear to undergo significant metabolism and because further downward reduction would result in AEGL-3 values below proposed AEGL-2 values and below non nonlethal concentrations in multiple-exposure studies in rats and dogs. Time scaling was accomplished using the default values of n =1 or n =3. During deliberations, a suggestion was made to calculate a $BMDL_{05}$ for the developmental effects proposed as the basis of AEGL-2. However, the raw data needed for this calculation were unavailable. After more discussion, a motion was made by George Rodgers and seconded by Susan Ripple to not recommend AEGL-1 values for HFA due to insufficient data. The motion carried (YES: 14; NO: 0; ABSTAIN: 0) (APPENDIX J). A motion was then made by Tom Hornshaw and seconded by Bob Benson to accept AEGL-3 values of 160 ppm, 160 ppm, 80 ppm, 20 ppm, and 10 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on the proposed POD of 200 ppm for 4 hours (NOEL for death in rats). Uncertainty factors of 3 each (total = 10) will be applied for inter- and intraspecies extrapolation. The justification for the intraspecies UF is as proposed above, and reducing the proposed interspecies UF from 10 to 3 is supported by multiple exposure studies in rats and dogs and the fact that HFA is not metabolized (is direct acting). Time scaling will be accomplished using n = 1, calculated by Marc Ruijten using the ten Berge program. The 30-min AEGL-3 value will be adopted as the 10-min value because the POD is ≥4 hours. The motion carried (YES: 15; NO: 1; ABSTAIN: 0) (APPENDIX J). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-2 values of 0.4 ppm, 0.4 ppm, 0.2 ppm, 0.05 ppm, and 0.025 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on the proposed POD of 1.0 ppm for 6 hours (developmental effects in rats). Uncertainty factor application and time scaling are the same as utilized for AEGL-3 derivation. An attempt will be made to obtain the raw data from the duPont study and calculate a $BMCL_{05}$ for the developmental toxicity data. Bob Young will report on this at a later meeting, and AEGL-2 values may be adjusted, if necessary. The motion carried (YES: 13; NO: 1; ABSTAIN: 3) (APPENDIX J).

Summary of AEGL Values for Hexafluoroacetone

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Appropriate data not available
AEGL–2	0.40 ppm	0.40 ppm	0.20ppm	0.05 ppm	0.025 ppm	NOEL for developmental effects in rats (duPont, 1989)
AEGL–3	160 ppm	160 ppm	80 ppm	20 ppm	10 ppm	NOEL for death in rats (duPont, 1962)

NR: Not Recommended because of insufficient data.

Aluminum Phosphide (CAS No. 20859-73-8)

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

Cheryl Bast reviewed the available data for aluminum phosphide, a solid (Attachment14). One mole of aluminum phosphide reacts rapidly with water or moisture in air to produce one mole of phosphine gas, and it is the phosphine gas that is responsible for acute toxicity. Appropriate chemical-specific data are not available for derivation of AEGL values for aluminum phosphide. In the absence of appropriate chemical-specific data for aluminum phosphide, the AEGL-2 and AEGL-3 values for phosphine were proposed as surrogates to obtain AEGL-2 and AEGL-3 values for aluminum phosphide, respectively. The use of phosphine as a surrogate for aluminum phosphide was deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from aluminum phosphide. It was proposed that the phosphine AEGL-2 values be adopted as AEGL-2 values for aluminum phosphide and the phosphine AEGL-3 values be adopted as AEGL-3 values for aluminum phosphide. Values will be expressed as ppm or mg/m^3 phosphine. AEGL-1 values are not recommended for aluminum phosphide because data were insufficient for derivation of AEGL-1 values for phosphine. After discussion, a motion was made by Bob Benson and seconded by John Hinz to adopt AEGL values as proposed. The motion passed (YES: 16; NO: 1; ABSTAIN: 1) (Appendix K).

It was then pointed out that seven additional metal phosphides are on the AEGL chemical priority list. A TSD for "Selected Metal Phosphides" will be prepared and presented at a future meeting. The aluminum phosphide values and analysis will be included in this TSD, and may be published in the same COT volume with the phosphine TSD.

Summary of AEGL Values for Aluminum Phosphide (EXPRESSED AS PPM OR MG/M^3 PHOSPHINE)*

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Appropriate data not available
AEGL-2	4.0 ppm (5.6 mg/m^3)	4.0 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.50 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)	Phosphine AEGL-2 values adopted as aluminum phosphide AEGL-2 values (NAC/AEGL, 2004).
AEGL-3	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.90 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)	Phosphine AEGL-3 values adopted as aluminum phosphide AEGL-3 values (NAC/AEGL, 2004).

NR: Not Recommended

Nitrogen Mustards
HN-1 (CAS No. 538-07-8)
HN-2 (CAS No. 5107502)
HN-3 (CAS No. 555-77-1)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Richard Thomas, INTERCET

Bob Young reviewed the available data for the nitrogen mustards (Attachment 15). No AEGL-1 values were proposed because of insufficient data and the absence of detection at exposures capable of causing toxic responses. Proposed AEGL-2 values for HN1, HN2, and HN3 were based upon the upper range of eye injury thresholds from studies with human volunteer subjects; 90, 55, and 42 mg-min/m^3, respectively, for HN1, HN2, and HN3. Proposed AEGL-2 values were: HN1: 0.90 ppm, 0.30 ppm, 0.15 ppm, 0.038 ppm, and 0.019 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN2: 0.55 ppm, 0.18 ppm, 0.092 ppm, 0.023 ppm, and 0.011 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN3: 0.42 ppm, 0.14 ppm, 0.070 ppm, 0.018 ppm, and 0.0088 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. The ocular response is likely independent of dosimetric processes that would be relevant to systemically-mediated toxicity. Therefore, the proposed uncertainty factor for individual variability was limited to 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects; therefore, modifying factor of 3 was applied to account for possible effects on the respiratory tract. Where AEGL-2 time points coincided with the exposure duration range used to establish the threshold Ct, time-specific exposure concentrations for proposed AEGLs were calculated from the Ct value. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 or 3 was used in the equation, $C^n \times t = k$, for extrapolating to AEGL time periods not within the range of experimental exposure duration.

Lethality thresholds (LCt_{50}) for rats were used as the basis for proposed AEGL-3 values; 860, 2000, and 670 mg-min/m^3 for HN1, HN2, and HN3, respectively. Proposed AEGL-3 values were: HN1: 2.9 ppm, 0.96 ppm, 0.48 ppm, 0.12 ppm, and 0.060 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN2: 6.7 ppm, 2.2 ppm, 1.1 ppm, 0.28 ppm, and 0.14 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN3: 2.2 ppm, 0.74 ppm, 0.37 ppm, 0.093 ppm, and 0.047 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively). These specific LCt_{50} values were based upon experimental exposure durations ranging from 20-100 minutes (HN1), 120-360 minutes (HN2), and 10-100 minutes (HN3) and, therefore considered suitable for AEGL development. Consistent with AEGL methodology (NRC, 2001), a three-fold reduction of these lethality values was used as an estimate of the lethality threshold and the point-of-departure for AEGL-3 development. A total uncertainty factor of 10 was applied. Adjustment for interspecies variability was limited to 3 because LCt_{50} values among multiple species (including nonhuman primates) did not appear to vary by more than three-fold for each agent, and the rat was somewhat more sensitive. Adjustment for individual variability was limited to 3 because the action of nitrogen mustards on cellular components would not be expected to greatly differ, and because additional downward adjustment would result in proposed AEGL-3 values inconsistent

with proposed AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard). An experimentally-derived *n* of 1 was used in the equation, $C^n \times t = k$, for extrapolating to AEGL time periods.

Marc Ruijten expressed concern with deriving AEGL values for these compounds because of the poor data base. He felt that this approach will set a precedence and will remove incentive for conducting new experiments and providing new data.

After discussion, a motion was made by Bob Benson and seconded by John Hinz to not recommend AEGL-1 values for HN1, HN2, and HN3. The motion passed unanimously by a show of hands. A motion was then made by George Rodgers and seconded by George Woodall to adopt AEGL-2 values for HN1 using the lower level of the range (37 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN1 of 0.37 ppm, 0.12 ppm, 0.062 ppm, 0.015 ppm, and 0.0077 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed. A motion was then made by George Woodall and seconded by George Rodgers to adopt AEGL-2 values for HN2 using the lower level of the range (40 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN2 of 0.13 ppm, 0.044 ppm, 0.012 ppm, 0.0056 ppm, and 0.0028 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed. A motion was then made by George Rodgers and seconded by Nancy Kim to adopt AEGL-2 values for HN3 using the lower level of the range (20 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN3 of 0.20 ppm, 0.067 ppm, 0.033 ppm, 0.0083 ppm, and 0.0042 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed. A motion was then made by Richard Thomas and seconded by Richard Niemier to adopt the most conservative set of AEGL-2 values (HN2 AEGL-2 values) as AEGL-2 values for all of the nitrogen mustards. All individually-derived chemical-specific values are to presented in an appendix to the TSD. The motion passed (YES: 12; NO: 1; ABSTAIN: 3) (Appendix L).

A motion was made by Richard Thomas and seconded by Richard Niemier to adopt AEGL-3 values for HN1 as proposed. The motion passed. A motion was then made by Richard Niemier and seconded by John Hinz to adopt the AEGL-3 values for HN2 and HN3 as proposed. The motion passed. Finally, a motion was made by Tom Hornshaw and seconded by Richard Niemier to adopt the most conservative set of AEGL-3 values (HN3 AEGL-3 values) as AEGL-3 values for all of the nitrogen mustards. All individually-derived chemical-specific values are to presented in an appendix to the TSD. The motion passed (YES: 10; NO: 1; ABSTAIN: 5) (Appendix L).

Summary of AEGL Values for Nitrogen Mustards						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not Recommended
AEGL–2	0.13 ppm	0.044 ppm	0.022 ppm	0.0056 ppm	0.0028 ppm	Lower limit of range for ocular irritation in humans sufficient to compromise operational effectiveness (Porton Report 1942a, 1943d; U.S. Army Med. Div. 1945c, d.)
AEGL–3	2.2 ppm	0.74 ppm	0.37 ppm	0.093 ppm	0.047 ppm	Lethality threshold in rats estimated as 3-fold reduction of LCt_{50} values (Porton Report. 1943b,c; U.S. Army Med. Div., 1945a)

Methylchlorosilane (CAS No. 993-00-0)

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

Cheryl Bast discussed the available data (Attachment 16). Methylchlorosilane reacts rapidly with water or moisture and decomposes to form hydrogen chloride gas. Complete hydrolysis of one mole of methylchlorosilane would yield a maximum of one mole of hydrogen chloride. No human or animal data on methylchlorosilane are available. Although chemical-specific data are not available for methylchlorosilane, data from structurally-similar alkyl-substituted silicon tetrahydrides [dimethyldichlorosilane (Dow Corning, 1997a), methyltrichlorosilane (Dow Corning,1997b) , trimethylchlorosilane (Dow Corning, 1999a), and methyldichlorosilane (Dow Corning, 2001)] suggest that the acute toxicity of chlorosilanes is due to the hydrogen chloride hydrolysis product. These data suggest that the effects of hydrogen chloride and chlorosilanes are both quantitatively (based on molar equivalents of hydrogen chloride) and qualitatively (based on clinical signs) similar. Therefore, proposed AEGL-1, AEGL-2 and AEGL-3 values for methylchlorosilane were set equivalent to the hydrogen chloride AEGL-1, AEGL-2, and AEGL-3 values (NRC, 2004), respectively. This approach was considered valid because one mole of hydrogen chloride is produced for every mole of methylchlorosilane hydrolyzed. A motion was then made by Richard Thomas and seconded by Steve Barbee to adopt AEGL-1, AEGL-2 and AEGL-3 values as proposed, The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix M).

Summary of AEGL Values for Methyl chlorosilane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	Hydrogen Chloride AEGL-1 values adopted as methylchlorosilane AEGL-1 values (NRC, 2004)
AEGL–2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Hydrogen Chloride AEGL-2 values adopted as methylchlorosilane AEGL-2 values (NRC, 2004)
AEGL–3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	Hydrogen Chloride AEGL-3 values adopted as methylchlorosilane AEGL-3 values (NRC, 2004)

Methyldichlorosilane (CAS No. 75-54-7)

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

Cheryl Bast discussed the available human and animal data (Attachment 17). Methyldichlorosilane reacts vigorously and rapidly with water and decomposes to form hydrogen chloride; complete hydrolysis of one mole of methyldichlorosilane would yield a maximum of two moles of hydrogen chloride. In the absence of appropriate chemical-specific data for derivation of AEGL-1 and AEGL-2 values for methyldichlorosilane, a modification of the AEGL-1 and AEGL-2 values, respectively, for hydrogen chloride was proposed to derive AEGL-1 and AEGL-2 values for methyldichlorosilane. The use of hydrogen chloride as a surrogate for methyldichlorosilane was deemed appropriate because the hydrolysis product, HCl, is responsible for the acute toxicity. Since two moles of hydrogen chloride are produced for every mole of methyldichlorosilane hydrolyzed, a molar adjustment factor of 2 was applied to the hydrogen chloride AEGL-1 and AEGL-2 values to approximate proposed AEGL-1 and AEGL-2 values for methyldichlorosilane. Proposed AEGL-3 values were based on a calculated LC_{01} of 1400 ppm in rats exposed to methyldichlorosilane for 1 hour (Dow Corning, 2001). An uncertainty factor of 10 was proposed to account for interspecies variability since data for methyldichlorosilane were available for only one species and an uncertainty factor of 3 was proposed to account for sensitive human subpopulations. Time scaling was accomplished using n = 1 (experimentally-derived value for HCl) for periods up to 4-hr. The 4-hour AEGL-3 value was adopted as the 8-hour value because time scaling would yield an 8-hour AEGL-3 value inconsistent with the total data set. After discussion, a motion to accept the AEGL values as

proposed was made by Richard Niemier and seconded by John Hinz. The motion carried (YES: 12; NO: 2; ABSTAIN: 0) (Appendix N).

Summary of AEGL Values for Methyldichlorosilane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	Modification of Hydrogen Chloride AEGL-1 values (NRC, 2004)
AEGL–2	50 (235)	22 (103)	11(52)	5.5 (26)	5.5 (26)	Modification of Hydrogen Chloride AEGL-2 values (NRC, 2004)
AEGL–3	280 (1316)	93 (437)	47 (220)	12 (56)	12 (56)	1 hour LC_{01} in rats (Dow Corning, 2001)

Diketene (CAS No. 674-82-8)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Warren Jederburg, U.S. Navy

Kowetha Davidson discussed the available data (Attachment 18). After some discussion, a motion was made by George Rodgers and seconded by George Woodall to Table this chemical until the September, 2005, NAC meeting when the structurally-similar chemical, ketene, is scheduled for presentation. Also, the BMC concentrations for diketene will be recalculated using the analytical, not nominal concentrations. The motion carried (YES: 15; NO: 0; ABSTAIN: 0) (Appendix O).

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-37: June 13-15, 2005, Washington DC
NAC/AEGL-38: September 28-30, 2005, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Bob Young, Oak Ridge National Laboratory, 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-36 Meeting Agenda
Attachment 2. NAC/AEGL-36 Attendee List
Attachment 3. SOP Issues
Attachment 4. PBPK White Paper
Attachment 5. Revised Chemical Priority List
Attachment 6. Response to Federal Register comments for epichlorohydrin
Attachment 7. Response to Federal Register comments for acetone
Attachment 8. Response to COT comments for allyl alcohol
Attachment 9. Response to COT comments for iron pentacarbonyl
Attachment 10. Response to COT comments for ammonia
Attachment 11. Response to COT comments for acrylic acid
Attachment 12. Data analysis for methyl t-butyl ether
Attachment 13. Data analysis for hexafluoroacetone
Attachment 14. Data analysis for aluminum phosphide
Attachment 15. Data analysis for nitrogen mustards
Attachment 16. Data analysis for methylchlorosilane
Attachment 17. Data analysis for methyldichlorosilane
Attachment 18. Data analysis for diketene

LIST OF APPENDICES

Appendix A. Ballot for final meeting highlights of NAC/AEGL-35
Appendix B. Final meeting highlights of NAC/AEGL-35
Appendix C. Ballot for exponent, n
Appendix D. Ballot for epichlorohydrin
Appendix E. Ballot for acetone
Appendix F. Ballot for iron pentacarbonyl
Appendix G. Ballot for ammonia
Appendix H. Ballot for acrylic acid
Appendix I. Ballot for methyl t-butyl ether
Appendix J. Ballot for hexafluoroacetone
Appendix K. Ballot for aluminum phosphide
Appendix L. Ballot for nitrogen mustards
Appendix M. Ballot for methylchlorosilane
Appendix N. Ballot for methyldichlorosilane
Appendix O. Ballot for diketene

NAC/AEGL Meeting 37: June 13-15, 2005

Minutes Approval

Appendix B

Chemical: **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA	UNANIMOUS APPROVAL				
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: KIM **Second by:** HINZ
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/13/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix C

Chemical: Send BACK WHITE PAPER TO NAS **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** X

Chemical Manager: X **Staff Scientist:** Claudia Troxel (W. JIM DENNISON, MANAGER)

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee	Y				Nancy Kim	Y			
Lynn Beasley	Y				Glenn Leach	Y			
Robert Benson	Y				John Morawetz	P			
Jonathan Borak	A				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	A			
George Cushmac	Y				Susan Ripple	Y			
Ernest Falke	A				George Rodgers	A			
Alfred Feldt	Y				Marc Ruijten	Y			
John Hinz	Y				George Rusch, Chair	Y			
Jim Holler	Y				Richard Thomas	A			
Tom Hornshaw	Y				George Woodall	Y			
Warren Jederberg	A								
					TALLY				
					PASS/ FAIL	16/16			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: S. Ripple **Second by:** G. Woodall
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/15/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix D

Chemical: SULFUR DIOXIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** NAS comments

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y		
Lynn Beasley	Y	Y		
Robert Benson	Y	Y		
Jonathan Borak	A	A		
William Bress	Y	Y		
George Cushmac	Y	Y		
Ernest Falke	Y	Y		
Alfred Feldt	Y	Y		
John Hinz	Y	Y		
Jim Holler	Y	Y		
Tom Hornshaw	Y	Y		
Warren Jederberg	A	A		

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y		
Glenn Leach	Y	Y		
John Morawetz	Y	Y		
Richard Niemeier	Y	Y		
Marinelle Payton	Y	Y		
Susan Ripple	A	A		
George Rodgers	A	A		
Marc Ruijten	P	P		
George Rusch, Chair	Y	Y		
Richard Thomas	A	A		
George Woodall	Y	Y		
TALLY				
PASS/ FAIL	17/17	17/17		

~~PPM, (mg/m³)~~	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(.30)	,(0.20)	,(0.20)	,(0.20)	,(0.20)
AEGL 2	,(.75)	,(0.75)	,(0.75)	,(0.75)	,(0.75)
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Barbee **Second by:** Hinz
AEGL 2 **Motion by:** Barbee **Second by:** Hinz
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/13/05

Appendix E

Chemical: CHLOROFORM **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** NAS RETURN for AEGL-3

Chemical Manager: **Staff Scientist:** Bob Young

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee			A		Nancy Kim			P	
Lynn Beasley			Y		Glenn Leach			Y	
Robert Benson			Y		John Morawetz			Y	
Jonathan Borak			A		Richard Niemeier			Y	
William Bress			Y		Marinelle Payton			Y	
George Cushmac			Y		Susan Ripple			P	
Ernest Falke			Y		George Rodgers			A	
Alfred Feldt			A		Marc Ruijten			P	
John Hinz			Y		George Rusch, Chair			Y	
Jim Holler			Y		Richard Thomas			A	
Tom Hornshaw			Y		George Woodall			Y	
Warren Jederberg			A						
					TALLY				
					PASS/ FAIL			14/14	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	[redacted],(4000)	[redacted],(4000)	[redacted],(3200)	[redacted]2000)	[redacted],(1600)
LOA					
* = ≥ 10% LEL					
** = ≥ 50% LEL					
*** = ≥ 100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:**_____ **Second by:**_____
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:** Bob Benson **Second by:** J. Heinz
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair:_____ **DFO:** [signature] **Date:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix F

Chemical: CARBON TETRACHLORIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** NAS Bring Back

Chemical Manager: Bill Bress **Staff Scientist:** Bob Young

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Alfred Feldt	A	A	A	
John Hinz	P	P	P	
Jim Holler	Y	Y	Y	
Tom Hornshaw	N	N	N	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	P	P	P	
Glenn Leach	Y	Y	Y	
John Morawetz	N	N	N	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	A	A	A	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	P	P	P	
Richard Thomas	A	A	A	
George Woodall	N	N	N	
TALLY				
PASS/ FAIL	11/14	11/14	11/14	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	58 ,( )	58 ,( )	44 ,( )	25 ,( )	19 ,( )
AEGL 2	380 ,( )	250 ,( )	190 ,( )	100 ,( )	81 ,( )
AEGL 3	1000 ,( )	690 ,( )	500 ,( )	300 ,( )	230 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: Falke **Second by:** B. Bress
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix G

Chemical: ALLYL ALCOHOL **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** REVISIT W/ OUT COMMENTS (AEGL-3 ONLY)

Chemical Manager: NANCY KIM **Staff Scientist:** CLAUDIA TROXEL

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee			Y		Nancy Kim			Y	
Lynn Beasley			Y		Glenn Leach			Y	
Robert Benson			P		John Morawetz			Y	
Jonathan Borak			A		Richard Niemeier			P	
William Bress			Y		Marinelle Payton			A	
George Cushmac			Y		Susan Ripple			Y	
Ernest Falke			A		George Rodgers			A	
Alfred Feldt			Y		Marc Ruijten			P	
John Hinz			Y		George Rusch, Chair			Y	
Jim Holler			Y		Richard Thomas			A	
Tom Hornshaw			P		George Woodall			Y	
Warren Jederberg			A						
					TALLY				
					PASS/ FAIL			13/13	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	36 ,( )	25 ,( )	20 ,( )	10 ,( )	10 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by:_____ **Second by:**_____
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by: Woodall **Second by:** Hinz
LOA Motion by:_____ **Second by:**_____

Approved by Chair:_____ **DFO:** Paul S. Tobin **Date:** 6/15/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix H

Chemical: XYLENE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** Bring back for modeling (HAS)

Chemical Manager: Bob Benson **Staff Scientist:** Claudia Troxel (W. JIM DEMISON, MODELER)

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	A	A	A	
Alfred Feldt	Y	Y	Y	
John Hinz	P	P	P	
Jim Holler	Y	Y	Y	
Tom Hornshaw	P	P	P	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	P	P	P	
Glenn Leach	Y	Y	Y	
John Morawetz	Y	N	P	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	A	A	A	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	A	A	A	
George Woodall	P	P	P	
TALLY				
PASS/ FAIL	13/13	12/13	12/12	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	130 ,( )	130 ,( )	130 ,( )	130 ,( )	130 ,( )
AEGL 2	2500 ,( )	1300 ,( )	920 ,( )	500 ,( )	400 ,( )
AEGL 3	7200 ,( )	3600 ,( )	2500 ,( )	1300 ,( )	1000 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: ↑ **Second by:** ↑
AEGL 2 Motion by: Bob Benson **Second by:** B. Braun
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/15/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix I

Chemical: BROMINE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	A			
Lynn Beasley	Y			
Robert Benson	Y			
Jonathan Borak	A			
William Bress	Y			
George Cushmac	Y			
Ernest Falke	Y			
Alfred Feldt	Y			
John Hinz	Y			
Jim Holler	Y			
Tom Hornshaw	Y			
Warren Jederberg	A			

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y			
Glenn Leach	Y			
John Morawetz	Y			
Richard Niemeier	Y			
Marinelle Payton	P			
Susan Ripple	Y			
George Rodgers	A			
Marc Ruijten	Y			
George Rusch, Chair	Y			
Richard Thomas	A			
George Woodall	Y			
TALLY				
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0,033 ,( )	0,033 ,( )	0,033 ,( )	0,033 ,( )	0,033 ,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Benson **Second by:** Moravetz
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** June 13, 2005

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: MAGNESIUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee	Y				Nancy Kim	Y			
Lynn Beasley	Y				Glenn Leach	Y			
Robert Benson	Y				John Morawetz	P			
Jonathan Borak	A				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	Y			
George Cushmac	Y				Susan Ripple	Y			
Ernest Falke	Y				George Rodgers	A			
Alfred Feldt	A				Marc Ruijten	Y			
John Hinz	Y				George Rusch, Chair	Y			
Jim Holler	Y				Richard Thomas	A			
Tom Hornshaw	Y				George Woodall	Y			
Warren Jederberg	A								
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	2.0 ,( )	2.0 ,( )	1.0 ,( )	0.25 ,( )	0.13 ,( )
AEGL 3	3.6 ,( )	3.6 ,( )	1.8 ,( )	0.45 ,( )	0.23 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** R. NIEMEIER **Second by:** S. RIPPLE
AEGL 2 **Motion by:** _____ **Second by:** _____
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: ALUMINUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	4.9, ( )	4.0, ( )	2.0, ( )	0.50, ( )	0.25, ( )
AEGL 3	7.7, ( )	7.2, ( )	3.6, ( )	0.90, ( )	0.45, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: POTASSIUM PHOSPHITE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	4.0 ,( )	4.0 ,( )	2.0 ,( )	0.50 ,( )	0.25 ,( )
AEGL 3	7.2 ,( )	7.2 ,( )	3.6 ,( )	0.90 ,( )	0.45 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: SODIUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	4.0, ( )	4.0, ( )	2.0, ( )	0.50, ( )	0.25, ( )
AEGL 3	9.2, ( )	7.2, ( )	3.6, ( )	0.90, ( )	0.45, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: ZINC PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	2.0 ,( )	2.0 ,( )	1.0 ,( )	0.25 ,( )	0.13 ,( )
AEGL 3	3.6 ,( )	3.6 ,( )	1.8 ,( )	0.45 ,( )	0.23 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: CALCIUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	2.0, ( )	2.0, ( )	1.0, ( )	0.25, ( )	0.13, ( )
AEGL 3	3.6, ( )	3.6, ( )	1.8, ( )	0.45, ( )	0.23, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: STRONTIUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	2.0, ( )	2.0, ( )	1.0, ( )	0.25, ( )	0.13, ( )
AEGL 3	3.6, ( )	3.6, ( )	1.8, ( )	0.45, ( )	0.23, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: MAGNESIUM ALUMINUM PHOSPHIDE **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR ,( )	NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	[redacted] 1.3 ,( )	[redacted] ,(1.3)	[redacted] ,(0.67)	[redacted] ,(0.17)	[redacted] ,(0.080)
AEGL 3	[redacted] 2.4 ,( )	[redacted] ,(2.4)	[redacted] ,(1.2)	[redacted] 0.30 ,( )	[redacted] ,(0.15)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

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:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix K

Chemical: DIMETHYLAMINE **CAS Reg. No.:** 124-40-3

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: E. FALKE **Staff Scientist:** A. MASLENNIKOV

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	AB	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	P	
Alfred Feldt	Y	Y	Y	
John Hinz	P	Y	Y	
Jim Holler	Y	Y	Y	
Tom Hornshaw	Y	Y	Y	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	P	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Y	Y	Y	
Susan Ripple	A	A	A	
George Rodgers	A	A	A	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	A	A	A	
George Woodall	P	Y	Y	
TALLY				
PASS/ FAIL	15/15	18/18	17/17	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10, ( )	10, ( )	10, ( )	10, ( )	10, ( )
AEGL 2	[redacted], (130)	[redacted] 85, ( )	[redacted], (66)	[redacted] 40, ( )	[redacted] 32, ( )
AEGL 3	480, ( )	320, ( )	250, ( )	150, ( )	120, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.

** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

gas, V.Sol. H_2O, BP 7.4°C, odor threshold .00076 - 1.6 ppm, LC50 ~ 4700 @ 4 HR RAT

NR= Not Recommended due to_____

AEGL 1 **Motion by:** MARC RUIJTEN **Second by:** R. NIEMEIER

AEGL 2 **Motion by:** MARC RUIJTEN **Second by:** Bob Benson

AEGL 3 **Motion by:** M. RUIJTEN **Second by:** John Hinz

LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/13/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix L

Chemical: METHYLAMINE **CAS Reg. No.:** 74-89-5

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: MARQUEA KING **Staff Scientist:** LYUDMILA TOCHILKINA ~~MARQUEA KING~~

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	A	
Robert Benson	Y	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	N	Y	
Alfred Feldt	Y	Y	Y	
John Hinz	Y	Y	Y	
Jim Holler	Y	Y	Y	
Tom Hornshaw	Y	Y	Y	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	A	A	A	
John Morawetz	Y	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Y	Y	Y	
Susan Ripple	Y	Y	Y	
George Rodgers	A	A	A	
Marc Ruijten	Y	P	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	A	A	A	
George Woodall	Y	P	Y	
TALLY				
PASS/ FAIL	18/18	15/16	17/17	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	15 ,( )	15 ,( )	15 ,( )	15 ,( )	15 ,( )
AEGL 2	160 ,( )	92 ,( )	64 ,( )	31 ,( )	21 ,( )
AEGL 3	~~410~~ ,( )	~~510~~ ,(510)	~~350~~ ,(350)	~~170~~ ,(170)	~~110~~ ,(110)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: MARC RUIJTEN **Second by:** R. NIEMEIER
AEGL 2 Motion by: B Benson **Second by:** R NIEMEIER
AEGL 3 Motion by: Niemeier **Second by:** Hinz
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/13/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix M

Chemical: TRIMETHYLAMINE **CAS Reg. No.:** 75-50-3

Action: Proposed X **Interim** _____ **Other** _____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	P	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	
Alfred Feldt	A	A	A	
John Hinz	Y	Y	Y	
Jim Holler	Y	Y	Y	
Tom Hornshaw	Y	Y	Y	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	P	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	N	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	P	Y	Y	
Susan Ripple	Y	Y	Y	
George Rodgers	A	A	A	
Marc Ruijten	P	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	A	A	A	
George Woodall	Y	Y	Y	
TALLY				
PASS/ FAIL				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	8.0 ,( )	8.0 ,( )	8.0 ,( )	8.0 ,( )	8.0 ,( )
AEGL 2	240 ,( )	150 ,( )	120 ,( )	[redacted]67 ,( )	[redacted]51 ,( )
AEGL 3	750 ,( )	490 ,( )	380 ,( )	220 ,( )	170 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1 **Motion by:** Tom Hornshaw **Second by:** E. Falke
AEGL 2 **Motion by:** M. Ruijten **Second by:** E. Falke
AEGL 3 **Motion by:** B. Benson **Second by:** S. Barbee
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** Paul Stolz **Date:** June 14, 2005

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: ETHYLAMINE **CAS Reg. No.:** 75-04-7

Action: Proposed X **Interim** _____ **Other** _____

Chemical Manager: MARQUEA KING **Staff Scientist:** VALERY KIRYUKHIN

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
~~Jonathan Borak~~	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Alfred Feldt	A	A	Y	
John Hinz	Y	Y	Y	
Jim Holler	Y	Y	Y	
Tom Hornshaw	Y	Y	Y	
~~Warren Jederberg~~	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	P	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Y	Y	Y	
~~Susan Ripple~~	*Y	*Y	A P	
~~George Rodgers~~	A	A	A	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
~~Richard Thomas~~	A	A	A	
George Woodall	Y	Y	Y	
TALLY				
PASS/ FAIL	17/17	18/18	18/18	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	7.5 ,( )	7.5 ,( )	7.5 ,( )	7.5 ,( )	7.5 ,( )
AEGL 2	150 ,( )	76 ,( )	49 ,( )	22 ,( )	14 ,( )
AEGL 3 (n = 1.6)	810 ,( )	420 ,( )	270 ,( )	120 ,( )	76 ,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1	Motion by: _____	Second by: _____
AEGL 2	Motion by: Tom Hornshaw	Second by: N. Niemeier
AEGL 3	Motion by: RUIJTEN	Second by: BENSON
LOA	Motion by: Benson	Second by: Hornshaw

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/13/05

NAC/AEGL Meeting 37: June 13-15, 2005

Chemical: Amine LOAs **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other** Setting LOA for amines

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee					Nancy Kim				
Lynn Beasley					Glenn Leach				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Susan Ripple				
Ernest Falke					George Rodgers				
Alfred Feldt					Marc Ruijten				
John Hinz					George Rusch, Chair				
Jim Holler					Richard Thomas				
Tom Hornshaw					George Woodall				
Warren Jederberg									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.

** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

MA 0.56
DMA 0.53

TMA 0.00051
EA 0.74

NR= Not Recommended due to_____

AEGL 1 Motion by: RUIJTEN **Second by:** BENSON
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair:_____ **DFO:** Paul S. Tobin **Date:** 6/15/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix P

Chemical: BIS(CHLOROMETHYL) ETHER **CAS Reg. No.:**

Action: Proposed X **Interim**_____ **Other**_____

Chemical Manager: ERNEST FALKE **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee	Y	Y	Y		Nancy Kim	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
Robert Benson	Y	Y	Y		John Morawetz	Y	Y	Y	
Jonathan Borak	A	Y	Y		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	Y	Y	Y	
George Cushmac	Y	Y	Y		Susan Ripple	Y	Y	Y	
Ernest Falke	Y	Y	Y		George Rodgers	A	A	A	
Alfred Feldt	A	Y	Y		Marc Ruijten	Y	Y	Y	
John Hinz	Y	Y	Y		George Rusch, Chair	N	N	N	
Jim Holler	Y	Y	Y		Richard Thomas	A	A	A	
Tom Hornshaw	N	Y	Y		George Woodall	N	N	N	
Warren Jederberg									
					TALLY				
					PASS/ FAIL	15/17			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	0.055 ; ( )	0.055 ; ( )	0.044 ; ( )	0.028 , ( )	0.020 ; ( )
AEGL 3	0.23 ; ( )	0.23 ; ( )	0.18 ; ( )	0.11 , ( )	0.075 ; ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.

** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

Include # + ref. to cancer calc'n. for 10^{-4} + cancer risk at the above levels.

NR= Not Recommended due to_____

AEGL 1 Motion by: Rusch **Second by:** Benson

AEGL 2 Motion by: Rusch **Second by:** Benson

AEGL 3 Motion by: Rusch **Second by:** Benson

LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DEO:** Paul S. Tobin **Date:** 6/14/05

NAC/AEGL Meeting 37: June 13-15, 2005

Appendix Q

Chemical: CHLOROMETHYL METHYL ETHER **CAS Reg. No.:** 107-30-2

Action: Proposed_____ **Interim**_____ **Other** NIS BRING BACK

Chemical Manager: Ernie Falke **Staff Scientist:** Sylvia Milanez

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Steven Barbee	Y	Y	Y		Nancy Kim	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
Robert Benson	Y	Y	Y		John Morawetz	Y	Y	Y	
Jonathan Borak	A	A	A		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
George Cushmac	Y	Y	Y		Susan Ripple	Y	Y	Y	
Ernest Falke	Y	Y	Y		George Rodgers	A	A	A	
Alfred Feldt	A	A	A		Marc Ruijten	Y	Y	Y	
John Hinz	Y	Y	Y		George Rusch, Chair	N	N	N	
Jim Holler	Y	Y	Y		Richard Thomas	A	A	A	
Tom Hornshaw	Y	Y	Y		George Woodall	Y	Y	Y	
Warren Jederberg	A	A	A						
					TALLY				
					PASS/ FAIL	16/17	16/17	16/17	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	0.60, ( )	0.60, ( )	0.49, ( )	0.30, ( )	0.22, ( )
AEGL 3	2.6, ( )	2.6, ( )	2.0, ( )	1.3, ( )	0.93, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: R. Niemeier **Second by:** John Hinz
AEGL 2 Motion by: R. Niemeier **Second by:** J. Hinz
AEGL 3 Motion by: " **Second by:** "
LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/14/05

Appendix R

AEGL Committee Chairman Certification of Minutes

National Advisory Committee for AEGLs June 13-15, 2005 Meeting

I, Dr. George Rusch, certify that these Minutes for the June 13-15, 2005 meeting of the National Advisory Committee for the Development of Acute Exposure Guideline Levels represent a true and accurate representation of the conduct of the meeting.

Chairman: George Rusch, Ph.D.