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

June 14-16, 2004

Final Meeting-33 Highlights

Moevenpick Hotel
Voorburg, The Netherlands

INTRODUCTION

Dr. Marc Ruijten, NAC member, welcomed the group to The Netherlands and to the first international meeting of the NAC/AEGL. Dr. R.D. Woittiez, Director of the Environmental Risks and Safety Division, RIVM, also welcomed the group and presented an overview of the RIVM mission and the relevance of the AEGL process.

The draft NAC/AEGL-32 meeting highlights were reviewed. Ernest Falke explained that during NAC/AEGL-32, the incorrect point-of-departure for the stated rationale was used for calculating the AEGL-2 values for phenol. The correct values should be 29 ppm (instead of 47 ppm) for the 10- and 30-min values, 23 ppm (instead of 37 ppm) for the 1-hour value, and 15 ppm (instead of 23 ppm) for the 4-hour value. A motion was made by George Rodgers and seconded by Nancy Kim to correct the AEGL-2 values for phenol to reflect the appropriate point-of-departure. The motion passed (YES: 15; NO: 0; ABSTAIN: 2) (Appendix A). The modification was approved unanimously by a voice vote. A motion was made by Richard Niemier and seconded by Nancy Kim to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by a show of hands (Appendix B). The final version of the NAC/AEGL-32 meeting highlights is attached (Appendix C) and was distributed to the NAC/AEGL by e-mail.

A motion was made by Bob Snyder and seconded by George Rodgers to dedicate this first international meeting of the NAC/AEGL to the memory of Roger Garrett, whose hard work and vision helped make the AEGL program an international effort. The motion passed unanimously by a voice vote (Appendix D).

The highlights of the NAC/AEGL-33 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-33 Agenda.

REVIEW of PRIORITY CHEMICALS

LEWISITE-1 (L-1) (CAS Reg. No. 541-25-3)
LEWISITE-2 (L-2) (CAS Reg. No. 40334-69-8)
LEWISITE-3 (L-3) (CAS Reg. No. 40334-70-1)

Staff Scientist: Cheryl Bast, ORNL
Chemical manager: Warren Jederberg, U.S. Navy

Cheryl Bast emphasized that it was important to be mindful of the relative toxicity of the chloroarsenicals when developing AEGL values. Cheryl then discussed the database for the lewisite compounds (Attachment 3), pointing out that data available for lewisite-1 and the L-1, L-2, and L-3 mixture suggested similar toxicity.

AEGL-1 values were not recommended because of insufficient data. Proposed AEGL-2 values (1.7 mg/m^3 for 10-min, 0.53 mg/m^3 for 30-min, 0.29 mg/m^3 for 1-hour, 0.073 mg/m^3 for 4-hours, and 0.037 mg/m^3 for 8-hours) were based upon a 3-fold reduction in the AEGL-3 values; this was considered an estimate of a threshold for irreversible effects and considered appropriate given the extremely steep concentration-response curve. The proposed AEGL-3 values for lewisite-1 (L-1) were based on dog lethality data (Armstrong, 1923). Proposed points-of-departure were one-third of the 30-min LC_{50} for the 30-min AEGL-3 value, one-third of the 1-hr LC_{50} for the 1-hr AEGL-3 value, and one-third of the 4-hr LC_{50} for the 4-hr AEGL-3 value. The proposed 10-min and 8-hr AEGL-3 values were derived from the 1-hr point-of-departure by time-scaling using the $c^n \times t = k$ relationship, where n=1 based on regression analysis of dog LC_{50} data (7.5 min. to 240 min.). Interspecies and intraspecies uncertainty factors of 3 each were applied. Proposed lewisite-1 AEGL-3 values were 5.1 mg/m^3 for 10-min, 1.6 mg/m^3 for 30-min, 0.86 mg/m^3 for 1-hour, and 0.22 mg/m^3 for 4-hours, 0.11 mg/m^3 and 8-hours. It was proposed to adopt lewisite-1 AEGL values for lewisite-2 and lewisite-3.

After much discussion, a motion was made by Marc Ruijten and seconded by Richard Niemier to adopt AEGL-3 values for lewisite-1 based on LC_{01} values calculated from dog lethality data (Armstrong, 1923) utilizing the ten Berge program (calculated LC_{01} values were:38.7 mg/m^3 for 10-min, 14.0 mg/m^3 for 30-min, 7.4 mg/m^3 for 1-hour, 2.1 mg/m^3 for 4-hours, and 1.1 mg/m^3 for 8-hours) and applying inter- and intraspecies uncertainty factors of 3 each. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix E). A motion was then made by Bob Snyder and seconded by George Rodgers to derive AEGL-2 values for L-1 by taking one-third of the AEGL-3 values and also applying a modifying factor of 2 for the sparse data set for effects defined by AEGL-2. The motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix E). A motion was then made by Richard Thomas and seconded by George Woodall to not recommend AEGL-1 values for lewisite-1 because of insufficient data. The motion passed unanimously by a show of hands (Appendix E). A motion was then made by Richard Niemier and seconded by Susan Ripple to adopt the lewisite-1 values for the mixture of lewisite-1, lewisite-2, and lewisite-3. This motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix E).

Summary of AEGL Values for Lewisite-1 and the mixture of L-1, L-2, and L-3						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	0.65 $mg.m^3$	0.23 $mg.m^3$	0.12 $mg.m^3$	0.035 $mg.m^3$	0.018 $mg.m^3$	1/3 of AEGL-3 with MF
AEGL–3	3.9 $mg.m^3$	1.4 $mg.m^3$	0.74 $mg.m^3$	0.21 $mg.m^3$	0.11 $mg.m^3$	Dog LC_{01} values (Armstrong, 1923)

ADAMSITE (CAS Reg. No. 578-94-9) (DM)
METHYLDICHLOROARSINE (CAS Reg. No. 593-89-5) (MD)
ETHYLDICHLOROARSINE (CAS Reg. No. 598-14-1) (ED)
PHENYLDICHLOROARSINE (CAS Reg. No. 696 -28-6) (PD)
DIPHENYLCHLOROARSINE (CAS Reg. No. 712-48-1) (DA)

Staff Scientist: Robert Young, ORNL
Chemical manager: Warren Jederberg, U.S. Navy

The chemical review on the five chloroarsenical compounds was presented by Bob Young (Attachment 4).

Adamsite (DM)

The proposed AEGL-1 values for adamsite were based on irritation in human volunteers exposed to 20 mg/m^3 adamsite for 2 minutes (Gongwer et al.,1958). A factor of 3 was applied to estimate a threshold for irritation and an additional intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Time scaling utilized an empirically-derived exponent (*n*) of 0.71 based on tolerance limits of human volunteers (Lawson and Temple,1922; Craighill and Folkoff, 1922). Proposed AEGL-1 values for adamsite were 0.23 mg/m^3 for 10-min, 0.05 mg/m^3 for 30-min, 0.02 mg/m^3 for 1-hour, 0.0022 mg/m^3 for 4-hours, and 0.00083 mg/m^3 for 8-hours.

The proposed AEGL-2 values for adamsite were based on respiratory tract gross pathology in monkeys exposed to 291 mg/m^3 for 10-minutes or 77 mg/m^3 adamsite for 60-minutes (Striker et al., 1967b). An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 10 were proposed, and time scaling utilized the empirically-derived n of 0.71. Proposed AEGL-2 values for adamsite were 9.7 mg/m^3 for 10-min, 6.8 mg/m^3 for 30-min, 2.6 mg/m^3 for 1-hour, 0.36 mg/m^3 for 4-hours, and 0.14 mg/m^3 for 8-hours.

The proposed 10-minute AEGL-3 value for adamsite was based on severe pulmonary effects in monkeys exposed to 1708 mg/m^3 for 5 minutes (Striker et al., 1967); whereas, the proposed 30-

min, 1-, 4-, and 8-hour AEGL-3 values were based on the highest non-lethal exposure in monkeys (279 mg/m^3 for 46 minutes) (McNamara, et al., 1969). An intraspecies uncertainty factor of 3 and interspecies uncertainty factor of 10 were proposed, and time scaling utilized the empirically-derived n of 0.71. Proposed AEGL-3 values for adamsite were 21 mg/m^3 for 10-min, 17 mg/m^3 for 30-min, 6.4 mg/m^3 for 1-hour, 0.91 mg/m^3 for 4-hours, and 0.34 mg/m^3 for 8-hours.

After much discussion, a motion was made by Richard Niemier and seconded by Richard Thomas to accept the AEGL-1 values of 0.20 mg/m^3 for 10 minutes, 0.042 mg/m^3 for 30 minutes, 0.016 mg/m^3 for 1 hour, 0.0022 mg/m^3 for 4 hours, and 0.00084 mg/m^3 for 8 hours based on human tolerance to adamsite at 0.14 mg/m^3 for 60 minutes (Craighill and Folkoff, 1922). An intraspecies UF of 3 was applied and scaling across time utilized n=0.71. The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix F). A motion was then made by Bob Snyder and seconded by George Woodall to adopt the AEGL-2 values as proposed. This motion passed (YES: 15; NO: 1; ABSTAIN: 0) (Appendix F). A motion was then made by Steve Barbee and seconded by Bill Bress to adopt AEGL-3 values as proposed. This motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix F).

Summary of AEGL Values for Adamsite (DM)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.20 mg/m^3	0.042 mg/m^3	0.016 mg/m^3	0.0022 mg/m^3	0.00084 mg/m^3	Tolerance in humans (Craighill & Folkoff, 1922)
AEGL–2	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3	Respiratory tract gross pathology in monkeys (Striker et al., 1967b)
AEGL–3	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3	Severe pulmonary effects in monkeys (Striker et al., 1967). Highest concentration causing No deaths in monkey (McMamara et al., 1969)

Methyldichloroarsine (MD)

Data were insufficient for proposing development of AEGL-1 values. The proposed AEGL-2 values for MD were estimated as a three-fold reduction of the AEGL-3 values. The proposed AEGL-3 values for MD were developed using the multiple time-point dog lethality data provided by Allen et al. (1922) who reported LC_{50} values for 7.5, 15, 30, 60, and 120-minute exposure durations (815, 303, 125, 47, and 31 mg/m^3, respectively). The 7.5-minute value was proposed as the basis for the 10-minute AEGL-3 while the 120-minute LC_{50} was proposed as the basis for the 4-hr and 8-hr AEGL-3 values. These LC_{50} values were decreased 3-fold as an estimate of the

lethality threshold (NRC, 2001). Time scaling was performed using the empirically-derived exponent (*n*) of 0.82 from multiple time-point dog LC_{50} values of Allen et al. (1922). Proposed uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 3 accounted for individual variability in response to a direct-acting irritant Proposed AEGL-3 values for MD were 6.4 mg/m^3 for 10-min, 1.4 mg/m^3 for 30-min, 0.52 mg/m^3 for 1-hour, 0.15 mg/m^3 for 4-hours, and 0.06 mg/m^3 for 8-hours.

After discussion, a motion was made by George Rodgers and seconded by Bob Benson to accept AEGL-3 values of 1.9 mg/m^3 for 10 minutes, 0.42 mg/m^3 for 30 minutes, 0.16 mg/m^3 for 1 hour, 0.044 mg/m^3 for 4 hours, and 0.019 mg/m^3 for 8 hours. The rationale is the same as proposed except that the intraspecies uncertainty factor is 10, not 3, for a total UF of 100. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix G). A motion was then made by Richard Niemier and seconded by Steve Barbee to adopt the AEGL-2 values of one-third the AEGL-3 values. This motion passed (YES: 13; NO: 1; ABSTAIN: 2) (Appendix G). A motion was then made by Bob Benson and seconded by Richard Niemier to not recommend AEGL-1 values for MD because of insufficient data. This motion passed (YES: 14; NO: 0; ABSTAIN: 0) (Appendix G).

Summary of AEGL Values for Methyldichloroarsine (MD)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	0.63 mg/m^3	0.14 mg/m^3	0.053 mg/m^3	0.015 mg/m^3	0.0063 mg/m^3	1/3 AEGL-3 values
AEGL–3	1.9 mg/m^3	0.42 mg/m^3	0.16 mg/m^3	0.044 mg/m^3	0.019 mg/m^3	Estimated lethality threshold in dogs (Allen et al., 1922)

Ethyldichloroarsine (ED)

No AEGL-1 or AEGL-2 values were initially proposed for ED. AEGL-3 values for 10 and 30 minutes, and 1 hour were proposed based on a lethality threshold estimated as a 3-fold reduction of a mouse 10-minute LCt_{50} of 1555.5 mg • min/m^3 (equivalent to a 10-minute LC_{50} of 155.5 mg/m^3) (Hutchens et al., 1943). The proposed resulting point-of-departure was 51.8 mg/m^3. Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 3 (limited individual variability in response to a direct-acting irritant), and a modifying factor (MF) of 2 were proposed in the development of the AEGL-3 values. Time scaling from the 10-minute experimental time point to the 30- and 60-minute AEGL-3 time frames utilized a default *n* of 1 (NRC, 2001). Limited data and uncertainties in extrapolating to exposure durations 24-fold and

48-fold greater than the 10-minute experimental time frame, preclude development of the 4-hour and 8-hour AEGL-3 values. Proposed AEGL-3 values for ED were 0.86 mg/m^3 for 10-min,0.29 mg/m^3 for 30-min, and 0.14 mg/m^3 for 1 hour.

After discussion, a motion was made by Marc Ruijten and seconded by Richard Niemier to accept AEGL-3 values of 0.52 mg/m^3 for 10 minutes, 0.17 mg/m^3 for 30 minutes, and 0.086 mg/m^3 for 1 hour. The rationale is the same as proposed except that the intraspecies uncertainty factor is 10 (not 3), and the MF will be deleted. Thus, the total adjustment (UF) is 100. The motion also included adopting AEGL-2 values of one-third the AEGL-3 values and not recommending AEGL-1 values because of a lack of data. The motion passed (YES: 14; NO: 0; ABSTAIN: 1) (Appendix H).

Summary of AEGL Values for Ethyldichloroarsine (ED)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	0.17 mg/m^3	0.057 mg/m^3	0.029 mg/m^3	NR	NR	1/3 AEGL-3 values
AEGL–3	0.52 mg/m^3	0.17 mg/m^3	0.086 mg/m^3	NR	NR	Estimated lethality threshold in mice (Hutchens et al., 1943)

Phenyldichloroarsine (PD)

No AEGL-1 or AEGL-2 values were initially proposed for PD. The proposed AEGL-3 values for PD were derived by assuming a 3-fold reduction of the mouse 10-minute LC_{50} of 330 mg/m^3 reported by Allen et al. (1922) as an estimate of a lethality threshold (NRC, 2001). The resulting point-of-departure was 110 mg/m^3. Because no data were available with which to empirically derive an exponent for $C^n \times t = k$, a default of $n = 1$ was used for scaling from the 10-minute experimental value to longer AEGL-specific time periods. Due to the limited data and the uncertainties regarding extrapolation to exposure durations that are 24-fold and 48-fold greater than the 10-minute experimental time frame, the 4-hour and 8-hour AEGL-3 values were not recommended. Assuming similarity in activity to other dichloroarsines, uncertainty factors of 10 for interspecies variability (uncertainties in extrapolating from animal lethality to exposures resulting in human deaths) and 3 (limited individual variability in response to a direct-acting irritant), and a modifying factor (MF) of 2 were applied. Proposed AEGL-3 values for PD were 1.8 mg/m^3 for 10-min, 0.61 mg/m^3 for 30-min, and 0.31 mg/m^3 for 1 hour.

After discussion, a motion was made by George Rodgers and seconded by Richard Niemier to accept AEGL-3 values of 1.1 mg/m^3 for 10 minutes, 0.37 mg/m^3 for 30 minutes, and 0.18 mg/m^3

for 1 hour. The rationale is the same as proposed except that the intraspecies uncertainty factor is 10 (not 3), and the MF will be deleted. Thus, the total adjustment (UF) is 100. The motion also included adopting AEGL-2 values of one-third the AEGL-3 values and not recommending AEGL-1 values because of a lack of data. The motion passed (YES: 14; NO: 0; ABSTAIN: 2) (Appendix I).

Summary of AEGL Values for Phenyldichloroarsine (PD)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	0.37 mg/m^3	0.12 mg/m^3	0.061 mg/m^3	NR	NR	1/3 AEGL-3 values
AEGL–3	1.1 mg/m^3	0.37 mg/m^3	0.18 mg/m^3	NR	NR	Estimated lethality threshold in mice (Allen et al., 1922)

Diphenylchloroarsine (DA)

No AEGL-1 or AEGL-2 values were initially proposed for DA. The proposed AEGL-3 values for DA were based upon rat data MMW (1918) which are supported by similar findings in rabbits and cats (MMW, 1918). For rats, rabbits and cats, 30-minute exposure to 236 mg/m^3 and 60 minute exposure to 118 mg/m^3 did not result in the death of any of the animals (4 rats and rabbits/group, 2 to 4 cats/group). These 10-minute data were used as the proposed point-of-departure for the 10 and 30-minute AEGL-3 values for DA, while the 60-minute data point was proposed for developing the 1-, 4-, and 8-hour AEGL-3 values for DA. Data were unavailable with which to derive a value for the exponent, *n*, in the equation $C^n \times t = k$. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1was used in extrapolating from the 60-minute experimental exposure period to the 4 and 8 hour AEGL-3 time periods, and an *n* of 3 was used for extrapolating from the 30-minute experimental period to the 10-minute AEGL-3 exposure. Proposed uncertainty factor adjustment consisted of 10 for interspecies variability due to uncertainties in extrapolating from animal lethality to exposures resulting in human deaths. An uncertainty factor of 3 was proposed to account for individual variability in response to a direct-acting irritant. A modifying factor of 2 was also applied to account for the limited data on DA; essentially only poorly described lethality studies were available. Proposed AEGL-3 values for DA were 5.7 mg/m^3 for 10-min, 3.9 mg/m^3 for 30-min, 2.0 mg/m^3 for 1-hour, 0.49 mg/m^3 for 4 hours and 0.25 mg/m^3 for 8 hours.

After discussion, a motion was made by Richard Niemier and seconded by Susan Ripple to accept AEGL-3 values of 3.4 mg/m^3 for 10 minutes, 2.4 mg/m^3 for 30 minutes, and 1.2 mg/m^3 for 1 hour, 0.30 mg/m^3 for 4 hours, and 0.15 mg/m^3 for 8 hours. The rationale is the same as proposed except that the intraspecies uncertainty factor is 10 (not 3), and the MF will be deleted. Thus, the total adjustment (UF) is 100. The motion also included adopting AEGL-2 values of one-third the

AEGL-3 values and not recommending AEGL-1 values because of a lack of data. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix J).

Summary of AEGL Values for Diphenylchloroarsine (DA)						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	1.1 mg/m^3	0.79 mg/m^3	0.039 mg/m^3	0.098 mg/m^3	0.049 mg/m^3	1/3 AEGL-3 values
AEGL–3	3.4 mg/m^3	2.4 mg/m^3	1.2 mg/m^3	0.30 mg/m^3	0.15 mg/m^3	No lethality threshold in cats, rats, rabbits (MMW, 1918)

Chloroacetone (CAS No. 78-95-5)

Chemical Manager: George Alexeeff, California EPA
Staff Scientist: Cheryl Bast, ORNL

The chemical review on chloroacetone was presented by Cheryl Bast (Attachment 5). AEGL-1 values were not proposed due to insufficient data. No robust data consistent with the definition of AEGL-2 were available. Therefore, the proposed AEGL-2 values for 30-minutes, 1-hour, and 4-hours were based upon a 3-fold reduction in the AEGL-3 values. The proposed 30-minute AEGL-2 value was proposed as the 10-minute AEGL-2 value because of a human case-report suggesting that exposure to 4.7 ppm caused immediate, severe irritation (Sargent et al., 1986); thus, it would be inappropriate to exceed this value at any time point. Also, the 4-hour AEGL-2 value was proposed as the 8-hour value; doing otherwise would drive the proposed 8-hour AEGL-2 value approximately 2-fold below occupational standards. The proposed AEGL-3 values were based on an estimated 1-hour male rat lethality threshold of 105 ppm (male $LC_{50} \div 3$) (Arts and Zwart, 1987). Interspecies and intraspecies uncertainty factors of 3 each were applied because chloroacetone is highly irritating and clinical signs are likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 was also supported by the fact that data suggest little species variability with regard to lethality from oral and dermal exposure to chloroacetone (rat oral LD_{50} values: 100-141 mg/kg; mouse oral LD_{50} values: 127-141 mg/kg; rabbit dermal LD_{50} = 141 mg/kg), and the 1-hr LC_{50} of 500 ppm for male and female rats (Arts and Zwart, 1987) gives an approximate dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 ml minute volume and a rat body weight of 250 g). The intraspecies uncertainty factor of 3 is also considered sufficient because data from the more sensitive males were used as the point-of-departure. Thus, the total adjustment was 10. Data were unavailable for an empirical derivation of *n* for chloroacetone. Therefore, an *n* of 3 was applied to extrapolate to the 10-minute and 30-minute time periods, and an *n* of 1 was applied to

extrapolate to the 4- and 8-hour time periods to provide AEGL values that would be protective of human health (NRC, 2001). Proposed AEGL-3 values were 19 ppm for 10-min, 13 ppm for 30-min, 11 ppm for 1-hour, 2.6 ppm for 4 hours and 1.3 ppm for 8 hours.

After discussion, a motion was made by Marc Ruijten and seconded by Bill Bress to adopt AEGL-3 values of 24 ppm for 10-min, 17 ppm for 30-min, 13 ppm for 1 hour, 3.3 ppm for 4 hours, and 3.3 ppm for 8 hours. The point-of-departure for these values was the 1-hour BMD_{05} of 131 ppm derived from male rat data (Arts and Zwart, 1987). Interspecies and intraspecies uncertainty factors of 3 each were applied. Time scaling used the default *n* values of 1 or 3, except that the 4 hour value was also adopted as the 8 hour value because time scaling to 8 hours would yield an 8-hour AEGL-3 value near occupational standards. The motion also included deriving AEGL-2 values for chloroacetone by dividing the AEGL-3 values by 3, and not recommending AEGL-1 values because of insufficient data. The motion passed (YES: 15; NO: 0; ABSTAIN: 1) (Appendix K).

Summary of AEGL Values for Chloroacetone						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	8.0 ppm	5.5 ppm	4.4 ppm	1.1 ppm	1.1 ppm	1/3 AEGL-3 values
AEGL–3	24 ppm	17 ppm	13 ppm	3.3 ppm	3.3 ppm	1-hour BMD_{05} for male rats (Arts and Zwart, 1987)

Hexane (CAS No. 110-54-3)

Staff Scientist: Peter Bos, RIVM
Chemical Manager: Al Feldt, U.S. DOE

The chemical review for hexane was presented by Peter Bos (Attachment 6). Proposed AEGL-1 values were based on a lack of CNS depression in mice exposed to 8000 ppm hexane for 5 minutes (Swann et al., 1974). An uncertainty factor of 3 was proposed, and time scaling using an *n* of 3 was proposed for extrapolation from the 5-minute POD to 10- and 30-minute AEGL-1 values. The resulting 30-min AEGL-1 value was proposed as the 1-, 4-, and 8-hour AEGL-1 values because steady-state is reached within 30 minutes. The proposed AEGL-1 values were 2100 ppm for 10-minutes, and 1500 ppm for 30-minutes, 1-, 4-, and 8-hours. The proposed AEGL-2 values were based on light anesthesia in mice exposed to 16,000 ppm for 5 minutes (Swann et al., 1974). Proposed uncertainty factor application and time scaling were the same as for AEGL-1. The

proposed AEGL-2 values were 4200 ppm for 10-minutes, and 2900 ppm for 30-minutes, 1-, 4-, and 8-hours. Proposed AEGL-3 values were based on no deaths in mice exposed to 32,000 ppm hexane for 5 minutes (Swann et al., 1974). Proposed uncertainty factor application and time scaling were the same as for AEGL-1. The proposed AEGL-3 values were 8500 ppm for 10-minutes, and 5900 ppm for 30-minutes, 1-, 4-, and 8-hours.

After discussion, a motion was made by Ernie Falke and seconded by Marc Ruijten to adopt hexane AEGL-3 values of 12,000 ppm for 10-minutes, and 8600 ppm for 30-minutes, 1-, 4-, and 8-hours. It was noted that the 10-min AEGL-3 value is >100% of the LEL, and that the 30-min, 1-, 4-, and 8-hour AEGL-3 values are >50% of the LEL. The point-of-departure was ataxia and decreased motor activity, but no deaths, in rats exposed to 86,200 ppm for 30 minutes (Raje et al., 1984). Inter- and intraspecies uncertainty factors of 3 each were applied (total =10) and time scaling from 30-min to 10-min was accomplished using an exponent of n = 3. The 30-min AEGL-3 value was adopted as the 1-, 4-, and 8-hour AEGL-3 values because steady-state is reached within 30 minutes. The motion passed (YES: 14; NO: 3; ABSTAIN: 0) (Appendix L). A motion was then made by Ernie Falke and seconded by Bob Benson to adopt AEGL-2 values of 4800 ppm for 10-minutes, and 3300 ppm for 30-minutes, 1-, 4-, and 8-hours. It was noted that the AEGL-2 values are >10% of the LEL. The point-of-departure was reduced respiration, associated with some narcosis, in rats exposed to 10,000 ppm for 6 hours (Bus et al., 1982). The point-of departure was considered a sub-AEGL-2 effect and is supported by repeated-exposure studies in rats showing no severe neurological effects in rats exposed at concentrations up to 24,000 to 48,000 ppm hexane. An uncertainty factor of 3 was applied and time scaling to the 10-min time point was accomplished using an exponent of n = 3. The 30-min AEGL-2 value was adopted as the 1-, 4-, and 8-hour AEGL-2 values because steady-state is reached within 30 minutes. The motion passed (YES: 15; NO: 0; ABSTAIN: 2) (Appendix L). A motion was then made by Bob Benson and seconded by Ernie Falke to not recommend AEGL-1 values for hexane due to insufficient data. The motion passed (YES: 15; NO: 0; ABSTAIN: 2) (Appendix L).

Summary of AEGL Values for Hexane

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	4800 ppm*	3300 ppm*	3300 ppm*	3300 ppm*	3300 ppm*	Reduced respiration, some narcosis in rats (Bus et al., 1982)
AEGL–3	**See below	***See below	***See below	***See below	***See below	Ataxia, decreased motor activity in rats, no death (Raje et al, 1984)

*The AEGL-2 values are higher than10% of the lower explosive limit of hexane in air (LEL = 1.1% (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

**[*]The 30–minute, 1-, 4-, and 8-hour AEGL-3 values are higher than 50% of the lower explosive limit of hexane in air (LEL = 1.1% (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated 10-minute, 1-, 4-, and 8-hour AEGL-3 values are constant at 8600 ppm.
[***]The 10–minute AEGL-3 value is higher than 100% of the lower explosive limit of hexane in air (LEL = 1.1% (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account. The calculated 10-minute AEGL-3 value is 12,000 ppm.

Methylene Chloride (CAS No. 75-09-2)

Staff Scientist: Peter Bos, RIVM
Chemical Manager: Bob Benson, U.S. EPA

Peter Bos presented a detailed discussion of the application of a physiologically-based pharmacokinetic model to derive AEGL values for DCM (Attachment 7). For the derivation of AEGL values, there are two endpoints of concern. The first being the concentration of DCM in the brain leading to CNS effects and the second being the production of carboxyhemoglobin from CO generated by metabolism of DCM. The NAC has previously discussed the effects of CO and is awaiting final comments on the TSD from the COT. Preliminary comments from the COT seemed to endorse the AEGL values presented. No AEGL-1 values are recommended for CO. The endpoint for AEGL-2 derivation for CO is 4% HbCO based on reduced time until onset of angina during physical exertion in patients with coronary artery disease. Because this is the most sensitive human population an UF of 1 is used. The endpoint for AEGL-3 derivation is 40-56% HbCO in healthy subjects causing no life-threatening symptoms. After application of an intraspecies uncertainty factor of 3, the endpoint is approximately 15% HbCO. The AEGL values for DCM must take into account the direct effects of DCM in the brain and the effects caused by HbCO.

Dr. Bos then presented a discussion of the construction and validation of the PBPK model which is a combination of the Andersen et al. (1991) model for the production of HbCO and the Reitz et al. (1997) model for the concentration of DCM in the brain. The model can be applied to rats or humans based on appropriate physiological factors, enzyme kinetics, and allometric scaling. An appendix to the TSD will describe all of the details of the model and its validation.

Dr. Bos presented a discussion of why the modeling is the preferred scientific approach for deriving AEGL values for DCM. A brief description follows. The metabolic pathway producing CO is non-linear with the external DCM concentration because the CYP2E1 saturates in the range of interest for AEGL values and there are known polymorphisms in glutathione S-transferase (GSSTT1-1). About 20% of Caucasians lack GSSTT1-1. These individuals will produce more HbCO at the same external concentration of DCM. The pharmacokinetic model incorporates these elements and can adequately predict the internal concentration of DCM in the brain and the concentration of HbCO as a function of the concentration of DCM in the ambient air and duration of exposure. The NAC unanimously endorsed application of the model to derive AEGL values. The NAC was of the opinion that the details of the model need not be presented to the NAC again.

However, those members who where not present could raise additional questions before the December meeting when the NAC will be asked to formally adopt proposed AEGL values.

The NAC endorsed the PBPK approach; therefore, Dr. Bos presented detailed application of the model and conditional AEGL values from the model runs (Attachment 8). As noted above the endpoints of concern are the DCM concentration in the brain and the % HbCO. Whichever endpoint occurred at the lower external DCM concentration for the time point of interest would determine the AEGL value. The NAC decided to vote on conditional values to provide information to committee members not present and to the public on how the model is used and the specific values derived. Dr. Bos will provide a revised TSD with all values included in the tables (that is values derived from CNS depression and from % HbCO for conjugators and non-conjugators). The document will be available before the September meeting but specific AEGL values will not be discussed. In the Federal Register Notice for the September meeting and at the meeting itself, the NAC and the public will be requested to provide written questions, comments, alternative approaches, etc. to Dr. Bos not later than October 31. Dr. Bos and his colleagues at RIVM will then have the opportunity to do the additional modeling required as it cannot be easily done at a meeting in a short time. At the December meeting, Dr. Bos will present a brief summary of the conditional values endorsed at the June meeting and respond to any comments received. The NAC may then formally adopt proposed AEGL values.

The AEGL-1 endpoint is a NOAEL for CNS effects following 1 hour exposure to humans at 514 ppm DCM (Stewart et al., 1972). This external exposure is equivalent to a concentration of 0.063 mM DCM in the human brain. Application of an intraspecies uncertainty factor of 3 gives a maximum target concentration of DCM in the human brain of 0.021 mM. The model was then used to calculate the time and external exposure necessary to give this internal concentration. The draft provisional values are 10 minute, 290 ppm; 30 minute, 230 ppm; 1 hour, 200 ppm; 4 hour 160 ppm; and 8 hour, 140 ppm. However because the values at 4 and 8 hours are at or above the AEGL-2 values for HbCO production, no AEGL-1 values will be recommended for 4 and 8 hours. A motion was made by George Woodall and seconded by Richard Thomas to accept these draft provisional AEGL-1 values for methylene chloride. The motion passed (YES: 15; NO: 0; ABSTAIN:2) (Appendix M). [For the purposes of comparison only, the values derived using the standard approach (1 hour exposure to 515 ppm, UF = 3, n = 3/1) are 10 minute, 310 ppm; 30 minute, 210 ppm; 1 hour, 170 ppm; 4 hour, 42 ppm; and 8 hour, 21 ppm.]

The AEGL-2 endpoint is a NOAEL for CNS effects (auditory vigilance and critical flicker frequency in humans from Winneke, 1974) at an exposure of 751 ppm for 230 minutes or 4% HbCO derived from the CO TSD as described above. For 10 and 30 minutes, the controlling endpoint is the DCM concentration in the human brain equivalent to 0.137 mM. An intraspecies UF of 1 was applied because the effects noted are sub AEGL-2 effects, the mechanism of action will not vary greatly among individuals as it is a direct effect of DCM, and because applying a larger UF will lead to unrealistic values in comparison with the human data available. For 1, 4, and 8 hours, the controlling endpoint is 4% HBCO concentration in non-conjugators. A motion was made by George Rodgers and seconded by George Woodall to accept draft, provisional AEGL-2 values as follows: 10 minutes, 1700 ppm; 30 minutes, 1200 ppm; 1 hour, 560 ppm; 4

hour, 100 ppm; and 8 hour, 60 ppm. The motion passed (YES: 12; NO: 2; ABSTAIN:3) (Appendix M).

The AEGL-3 endpoint is a NOAEL for mortality in rats exposed to 11,000 ppm for 4 hours (Haskell Laboratories, 1982) or 15% HbCO derived from the CO TSD as described above. For 10 and 30 minutes, and 1 and 4 hours the controlling endpoint is the DCM concentration in the rat brain of 3.01 mM. After application of an interspecies UF of 1 because the susceptibility between species is small and the human PBPK model is used, and an intraspecies UF of 3 because the mechanism of action (CNS-depression) will not vary greatly among individuals, the endpoint is a concentration of DCM in the human brain of 1.0 mM (3.01 mM divided by 3). At 8 hours the controlling endpoint is 15% HbCO in non-conjugators. A motion was made by Bob Snyder and seconded by Ernie Falke to accept draft provisional AEGL-3 values as follows: 10 minutes, 12,000 ppm; 30 minutes, 8500 ppm; 1 hour, 6900 ppm; 4 hour, 4900 ppm; and 8 hour, 2100 ppm. The motion passed (YES: 14; NO: 0; ABSTAIN:3) (Appendix M).

A motion was then made by Bob Snyder and seconded by George Rodgers that if data are appropriate and a model is available, the NAC will use the PBPK for derivation of AEGL values. The motion passed unanimously by a show of hands (Appendix N).

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

Staff Scientist: Johan Schefferlie, Netherlands
Chemical Manager: Nancy Kim

Johan Schefferlie presented the chemical review on sulfuric acid, sulfur trioxide, and oleum (Attachment 9). These three chemicals are presented together in one TSD. The proposed AEGL-1 values for sulfuric acid were based on a NOEL for respiratory irritation in exercising asthmatics (Horvath et al., 1982; Avol et al., 1979). The proposed AEGL-1 value for sulfuric acid was 0.1 mg/m^3 for all time points. The proposed AEGL-2 values for sulfuric acid were based on termination of exercise in 4 of 19 human subjects exposed to 2.0 mg/m^3 for 60 minutes (Linn et al., 1989). The proposed AEGL-2 value for sulfuric acid was 2.0 mg/m^3 for all time points. The proposed AEGL-3 values for sulfuric acid were based on LC_{01} values for 10-min, 30-min, 1-hr, 4-hr, and 8-hr calculated from probit analysis of mouse lethality data (Runcle and Hahn, 1976). No interspecies uncertainty factor was proposed because mice are more sensitive than rats and rabbits, monkeys did not die and did not show serious effects when exposed to 502 mg/m3 for 7 days, and because occupational concentrations up to 35 mg/m^3 were tolerated during work shifts without severe effects. An intraspecies uncertainty factor of 3 was proposed. Proposed AEGL-3 values for sulfuric acid were 265 mg/m^3 for 10-minutes, 197 mg/m^3 for 30-minutes, 164 mg/m^3 for 1-hour, 113 mg/m^3 for 4-hours, and 93 mg/m^3 for 8-hours. Proposed time scaling for AEGL-3 was

based on probit analysis of the animal lethality data (n=3.7), and AEGL-1 and AEGL-2 values were held constant across time because sulfuric acid is a direct acting irritant.

After much discussion, a motion was made by Richard Thomas and seconded by Nancy Kim to accept an AEGL-1 value for sulfuric acid of 0.2 mg/m^3 for all time points based on a weight of evidence approach from human studies showing no effects or only mild irritation. No uncertainty factor was applied. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix O). A motion was then made by Richard Niemier and seconded by Susan Ripple to accept an AEGL-2 for sulfuric acid of 8.7 mg/m^3 for all time points, based on the lower limit of worker monitoring studies showing no effects in exposed workers (26 mg/m^3). An uncertainty factor of 3 was applied to protect sensitive individuals. This motion passed (YES: 15; NO: 0; ABSTAIN: 2) (Appendix O). A motion was then made by Nancy Kim and seconded by Richard Thomas to adopt AEGL-3 values for sulfuric acid as proposed (with the exception that values will be rounded to two significant figures). The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (Appendix O). A motion was then made by Richard Niemier and seconded by Bill Bress to apply the sulfuric acid AEGL values to sulfur trioxide and oleum. This motion passed by a show of hands (Appendix O).

Summary of AEGL Values for Sulfuric Acid*

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	No effects or minor irritation in humans (weight of evidence)
AEGL–2	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	Lower limit of NOEL in occupationally-exposed workers (El-Sadik et al., 1972)
AEGL–3	270 mg/m^3	200 mg/m^3	160 mg/m^3	110 mg/m^3	93 mg/m^3	Mouse LC_{01} (Runcle and Hahn, 1976)

*AEGL values for sulfuric acid also apply to oleum and sulfur trioxide.

Special Presentation

George Woodall gave a special presentation on “Innovations in Risk Assessment.” The presentation focused on databases, and use of proteomics and genomics for risk assessment.

Administrative Matters

The site and time of future meetings is as follows:

NAC/AEGL-34: September 21-23, 2004, Washington DC
NAC/AEGL-35: December 13-15, 2004, Washington, D.C.

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

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-33 Meeting Agenda
Attachment 2. NAC/AEGL-33 Attendee List
Attachment 3. Data Analysis of lewisite compounds
Attachment 4. Data Analysis of chloroarsenical compounds
Attachment 5. Data Analysis of chloroacetone
Attachment 6. Data Analysis of hexane
Attachment 7. Application of PBPK model for methylene chloride
Attachment 8. PBPK model construction and validation for methylene chloride
Attachment 9. Data Analysis of oleum, sulfuric acid, and sulfur trioxide

LIST OF APPENDICES

Appendix A. Ballot for phenol point-of-departure modification
Appendix B. Ballot for approval of NAC/AEGL-32 meeting highlights
Appendix C. Final meeting highlights of NAC/AEGL-32
Appendix D. Ballot for dedicating NAC/AEGL-33 to the memory of Roger Garrett
Appendix E. Ballot for lewisite compounds
Appendix F. Ballot for adamsite
Appendix G. Ballot for methyldichloroarsine
Appendix H. Ballot for ethyldichloroarsine
Appendix I. Ballot for phenyldichloroarsine
Appendix J. Ballot for diphenylchloroarsine
Appendix K. Ballot for chloroacetone
Appendix L. Ballot for hexane
Appendix M. Ballot for methylene chloride
Appendix N. Ballot for use of PBPK method when appropriate
Appendix O. Ballot for sulfuric acid, oleum, and sulfur trioxide

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-33
June 14-16, 2004

Moevenpick Hotel
Voorburg, The Netherlands

AGENDA

Monday, June 14, 2004

9:00 a.m.	Welcome- Marc Ruijten
9:15	Introductory remarks and approval of NAC/AEGL-32 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
9:30	Review of Lewisite-1 (L-1), Lewisite-2 (L-2), and Lewisite- (L-3) (Warren Jederberg/Cheryl Bast)
10:30	Break
10:45	Review of Lewisite-1 (L-1), Lewisite-2 (L-2), and Lewisite- (L-3) (continued)
12:00 p.m.	Lunch
1:00	Review of Adamsite, diphenyl chloroarsine, Ethyl dichloroarsine, Methyl dichloroarsine, and Phenyl dichloroarsine (Warren Jederberg/ Bob Young)
3:00	Break
3:15	Review of Adamsite, diphenyl chloroarsine, Ethyl dichloroarsine, Methyl dichloroarsine, and Phenyl dichloroarsine (continued)
4:00	Review of Chloroacetone (George Alexeeff/Cheryl Bast)
5:30	Adjourn for the day

Tuesday, June 15, 2004

8:30 a.m.	Review of Hexane (Al Feldt/Peter Bos)
10:30	Break
10:45	Discussion of Methylene chloride PBPK issues (Bob Benson/Peter Bos)
12:15 p.m.	Lunch
1:15	Review of Sulfuric acid, Sulfur trioxide, and Oleum (Nancy Kim/J. Schefferlie)
3:15	Break
3:30	Review of Sulfuric acid, Sulfur trioxide, and Oleum (continued)
5:30	Adjourn for the day

Wednesday, June 16, 2004

8:00 a.m.	Approval of Footnotes for AEGL values (John Morawetz)
9:00	Discussion of Public Comments (If available): Carbon disulfide, 1,4-Dioxane, Acetone, Acrolein, Chloroform, Epichlorohydrin, Methyl mercaptan, n,n-Dimethylformamide, Nitric acid, Nitric oxide, Nitrogen dioxide, peracetic acid, Sulfur dioxide, Trichloroethylene, Trimethylchlorosilane
10:00	Break
10:15	Discussion of Public Comments (If available) (continued)
11:45	Administrative matters
12:00 noon	Adjourn meeting

ATTENDANCE 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

ATTACHMENT 2

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

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

Chemical Manager: Paul Tobin ✓ **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	X				Nancy Kim	N.K.			
Steven Barbee	SB				Glenn Leach	GJL			
Lynn Beasley	LAB				John Morawetz	X			
Robert Benson	RB				Richard Niemeier	RWN			
Jonathan Borak	X				Marinelle Payton	✓ → 11 AM			
William Bress	WB				Susan Ripple	SR			
George Cushmac	GEC				George Rodgers	GR			
Ernest Falke	EF				Marc Ruijten	MR			
Alfred Feldt	X				George Rusch, Chair	GMR			
John Hinz	X				Robert Snyder	RS			
Jim Holler	X				Richard Thomas	RBT			
Tom Hornshaw	X				George Woodall	GW			
Warren Jederberg	X								
					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.

IGOR PILIOS
BORIS FILATOV EDPNC
VLADIMIR TCHERNOV Chernov

URSULA STEPHAN Ursula Stephan
COR VAN DEN BOGAARD Cor van den Bogaard

NR= Not Recommended due to_____

Cheryl Bast - ORNL
Robert Young - ORNL

COR VAN DEN BOGAARD

AEGL 1 Motion by:_____ **Second by:** Marcel van Raaij
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

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

Nomenclature of Lewisite Agents		
Common Name	Military Designator	Chemical name
Lewisite-1	L (L-1)	2-chlorovinyldichloroarsine
Lewisite-2	L-2	*bis*-(2-chlorovinyl)chloroarsine
Lewisite-3	L-3	*tris*-(2-chlorovinyl)arsine

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

LEWISITE-1 (L-1)
LEWISITE-2 (L-2)
LEWISITE-3 (L-3)

NAC/AEGL-33
June 14-16, 2004
Voorburg, The Netherlands

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Warren Jederberg

Chemical Reviewers: Glenn Leach and Richard Thomas

Lewisite -1 (L or L-1) is formed by the reaction of acetylene with arsenic trichloride using aluminum trichloride as a catalyst.

Lewisite-2 and lewisite-3 are co-products concurrently formed with lewisite-1.

Lewisite-1 yield is >65%.

Lewisite-2 yield is approximately 7-10%

Lewisite-3 yield is approximately 4-12%

Arsenic trichloride is also formed.

Therefore, an accidental release from storage tanks of L-1 will likely be the release of a mixture of L-1, L-2, L-3, and arsenic trichloride.

L-2 and L-3 will be less significant than L-1:

Smaller quantities

Comparatively low volatility

The toxicity of L-2 and L-3 is reportedly comparable to L-1

Therefore, AEGL values for L-1 should be protective for L-2, L-3, and the mixture.

Toxicological data on arsenic trichloride are very limited. Qualitatively, effects are similar to those of L-1 (corrosiveness, damage to skin, eyes, and mucous membranes). Quantitatively with regard to lethality, arsenic trichloride appears to be approximately 2 to 3 times less toxic than L-1 (LCt_{50} for arsenic trichloride: 4000-5000 mg·min/m^3 ; LCt_{50} for L-1:1200-1500 mg·min/m^3) (Flury, 1921).

AEGL-1 VALUES: Lewisite-1 (L-1)				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Data were insufficient for derivation of AEGL-1 values for lewisite-1 (L-1).

AEGL-1 values for lewisite-1 (L-1) are Not Recommended (NR).

AEGL-2 VALUES: LEWISITE-1 (L-1)				
10 minute	30 minute	1 hour	4 hour	8 hour
1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3

Endpoint: Three-fold reduction of AEGL-3 values. Estimated threshold for the inability to escape.

Reference: Armstrong, 1923

Time Scaling: See AEGL-3 derivation.

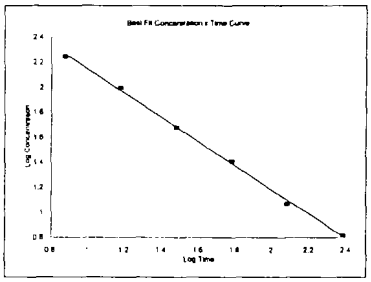
Uncertainty Factors:

Interspecies = 3 See AEGL-3 justification.

Intraspecies = 3 See AEGL-3 justification.

Time	Conc	Log Time	Log Conc	Regression Output:	
7.5	176	0.8751	2.2455	Intercept	3.1115
15	100	1.1761	2.0000	Slope	-0.9667
30	48	1.4771	1.6812	R Squared	0.9984
60	25.7	1.7782	1.4099	Correlation	-0.9992
120	11.8	2.0792	1.0719	Degrees of Freedom	4
240	6.6	2.3802	0.8195	Observations	6

n = 1.03
k = 1654.2



AEGL-3 VALUES: LEWISITE-1 (L-1)				
10 minute	30 minute	1 hour	4 hour	8 hour
5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3

Reference: Armstrong, 1923
Species: Dog(1-17/group)

Exposure: 126, 176, 231, 274, 330 mg/m^3 / 7.5 min.
68.7, 87.7, 96, 102, 125, 233 mg/m^3 / 15 min.
11.5, 24.5, 30.6, 41.5, 48, 58.6 mg/m^3 / 30 min.
5.8, 8, 25, 35, 43, 53 mg/m^3 / 1 hour
4.8, 12.5, 17.9, 24.5, 34.5 mg/m^3 / 2 hours
2.1, 6.2, 10, 16.9 mg/m^3 / 4 hours

Endpoints:
10-min, 1-hr, and 8-hr: 8.56 mg/m^3; ⅓ 1-hr LC_{50}; threshold for death.
30-min: 16 mg/m^3; ⅓ 30-min. LC_{50}; threshold for death.
4-hr: 6.24 mg/m^3; ⅓ 4-hr. LC_{50}; threshold for death.

Time Scaling: 10-min and 8-hr values derived from the 1-hr point-of-departure by time-scaling using the $c^n \times t = k$ relationship, where n=1 based on regression analysis of dog LC_{50} data (7.5 min. to 240 min.). 30-min, 1-hr, and 4-hr values derived from time period-specific data.

Uncertainty Factors:
Interspecies = 3 Little species variability with regard to lethality from inhalation exposure to lewisite-1; c x t values are relatively constant across species, except for the guinea pig, factor of 3 encompasses the 2 to 3-fold difference in sensitivity between guinea pigs and other species.

Intraspecies = 3 Steep concentration-response curve with regard to lethality implies limited intraspecies variation (10-min mouse LC_{50} = 200 mg/m^3, 10-min 100% mortality in mice = 240 mg/m^3; no mortality in dogs at 126 mg/m^3 for 7.5-min, LC_{50} = 176 mg/m^3)

AEGL-1 VALUES: Lewisite-2 (L-2)				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Data were insufficient for derivation of AEGL-1 values for lewisite-2 (L-2).

AEGL-1 values for lewisite-2 (L-2) are Not Recommended (NR).

AEGL-2 VALUES: LEWISITE-2 (L-2)				
10 minute	30 minute	1 hour	4 hour	8 hour
1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3

Reference: Armstrong, 1923

Endpoint: The AEGL-2 values for Lewisite-1 (L-1) are adopted as AEGL-2 values for Lewisite-2 (L-2).

Rationale:

Appropriate chemical-specific data were not available for derivation of AEGL-2 values for lewisite-2 (L-2).

L-2 exists as a small fraction of total lewisite (7 to 10%) and has a comparatively low volatility.

The toxicity of L-2 is reportedly comparable to L-1.

Because of these chemical characteristics, AEGL values for L-1 should be protective for L-2.

AEGL-3 VALUES: LEWISITE-2 (L-2)				
10 minute	30 minute	1 hour	4 hour	8 hour
5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3

Reference: Armstrong, 1923

Endpoint: The AEGL-3 values for Lewisite-1 (L-1) are adopted as AEGL-3 values for Lewisite-2 (L-2).

Rationale:

Appropriate chemical-specific data were not available for derivation of AEGL-3 values for lewisite-2 (L-2).

L-2 exists as a small fraction of total lewisite (7 to 10%) and has a comparatively low volatility.

The toxicity of L-2 is reportedly comparable to L-1.

Because of these chemical characteristics, AEGL values for L-1 should be protective for L-2.

AEGL-1 VALUES: Lewisite-3 (L-3)				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Data were insufficient for derivation of AEGL-1 values for lewisite-3 (L-3).

AEGL-1 values for lewisite-3 (L-3) are Not Recommended (NR).

AEGL-2 VALUES: LEWISITE-3 (L-3)				
10 minute	30 minute	1 hour	4 hour	8 hour
1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3

Reference: Armstrong, 1923

Endpoint: The AEGL-2 values for Lewisite-1 (L-1) are adopted as AEGL-2 values for Lewisite-3 (L-3).

Rationale:

Appropriate chemical-specific data were not available for derivation of AEGL-2 values for lewisite-3 (L-3).

L-3 exists as a small fraction of total lewisite (4 to 12%) and has a comparatively low volatility.

The toxicity of L-3 is reportedly comparable to L-1.

Because of these chemical characteristics, AEGL values for L-1 should be protective for L-3.

AEGL-3 VALUES: LEWISITE-3 (L-3)				
10 minute	30 minute	1 hour	4 hour	8 hour
5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3

Reference: Armstrong, 1923

Endpoint: The AEGL-3 values for Lewisite-1 (L-1) are adopted as AEGL-3 values for Lewisite-3 (L-3).

Rationale:

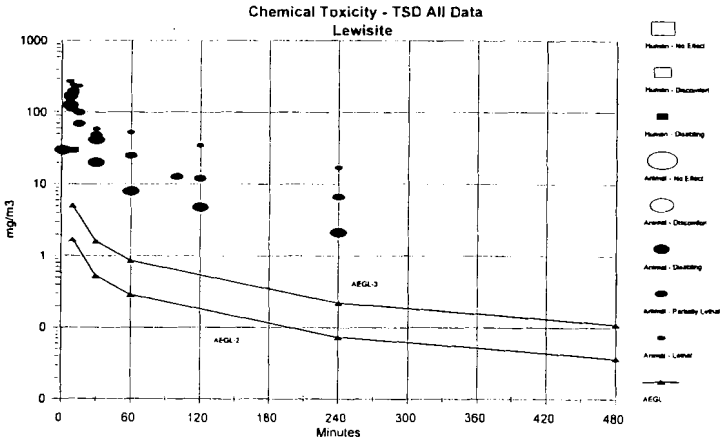
Appropriate chemical-specific data were not available for derivation of AEGL-3 values for lewisite-3 (L-3).

L-3 exists as a small fraction of total lewisite (4 to 12%) and has a comparatively low volatility.

The toxicity of L-3 is reportedly comparable to L-1.

Because of these chemical characteristics, AEGL values for L-1 should be protective for L-3.

Summary of AEGL Values for Lewisite Compounds (L-1, L-2, L-3)						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1						Insufficient data for derivation of AEGL-1 values
Lewisite-1 (L-1)	NR	NR	NR	NR	NR	
Lewisite-2 (L-2)	NR	NR	NR	NR	NR	
Lewisite-3 (L-3)	NR	NR	NR	NR	NR	
AEGL-2						⅓ of AEGL-3 values
Lewisite-1 (L-1)	1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3	L-1 AEGL-2 values
Lewisite-2 (L-2)	1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3	L-1 AEGL-2 values
Lewisite-3 (L-3)	1.7 mg/m^3	0.53 mg/m^3	0.29 mg/m^3	0.073 mg/m^3	0.037 mg/m^3	
AEGL-3						⅓ dog L-1 LC_{50} values (Armstrong, 1923)
Lewisite-1 (L-1)	5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3	L-1 AEGL-3 values
Lewisite-2 (L-2)	5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3	
Lewisite-3 (L-3)	5.1 mg/m^3	1.6 mg/m^3	0.86 mg/m^3	0.22 mg/m^3	0.11 mg/m^3	L-1 AEGL-3 values



ATTACHMENT 4

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

ADAMSITE (CAS Reg. No. 578-94-9) (DM)
PHENYLDICHLOROARSINE (CAS Reg. No. 696 -28-6) (PD)
ETHYLDICHLOROARSINE (CAS Reg. No. 598-14-1) (ED)
METHYLDICHLOROARSINE (CAS Reg. No. 593-89-5) (MD)
DIPHENYLCHLOROARSINE (CAS Reg. No. 712-48-1) (DA)

NAC/AEGL-33
June 14-16, 2004

Moevenpick Hotel
Voorburg, The Netherlands

TABLE 1. Nomenclature of Chloroarsenical Agents

Common name	Military Designator	Chemical name/Synonyms	CAS Registry No.
Adamsite	DM	diphenylaminechlorarsine; diphenylaminochloroarsine; diphenylaminechlororarsine; diphenylaminearsine 10-chloro-5, 10-dihydrochlorphenarsazine phenarsazine chloride 5-aza-10-arsenaanthracene chloride	578-94-9
Diphenylchloroarsine	DA	diphenylchloroarsine; diphenylarsinous chloride Clark I	712-48-1
Ethyldichloroarsine	ED	ethyldichloroarsine	598-94-9
Methyldichloroarsine	MD	methyldichloroarsine	593-89-5
Phenyldichloroarsine	PD	phenyldichloroarsine; dichlorophenylarsine phenyl-arsenous dichloride	696-28-6

NDRC (1946); Cookson and Nottingham (1969); USACHPPM (1996)

CHLOROARSENICAL AGENTS

- lacrymators, vomiting agents, sternutators
- biological activity due, in part, to affinity with sulfhydryl groups
- used primarily as riot control agents, harassing agents, incapacitating agents
- most data are from early military studies and reports

DATA SUMMARY - ADAMSITE (DM)

Human Experience

- odor detection: 2.5 mg/m^3
- ocular and nasopharyngeal irritation
- studies with human volunteers revealed tolerance limits of 3.1 - 90 mg - min/m^3 (encompassed concentrations of 3.1-90 mg/m^3 and exposure durations of 0.68 - 60 minutes (Lawson and Temple, 1922)
- ECt_{50} >100 mg - min/m^3 based upon tolerance limits for 30-sec. and 120-sec. exposures (Gongwer et al. 1958)
- 22-92 mg/m^3 for 1-min duration considered intolerable (McNamara et al., 1969)
- estimated LCt_{50} of 11,000 mg - min/m^3

DATA SUMMARY - ADAMSITE (DM)

Animal Data

Monkeys

Effects of Acute Exposure of Monkeys to Adamsite (DM) Aerosols.			
Exposure Concentration (mg/m^3)	Exposure Duration (min)	Ct ($mg \cdot min/m^3$)	Effects
855	3	2565	superficial tracheitis, edema of trachea and bronchial mucosa in one monkey at 12 hrs post exposure; no other effects noted for any monkeys at any examination time.
1708	5	8540	At 12 hrs bronchorrhea, focal pulmonary edema and congestion in 2 monkeys At 24 hrs, more pronounced edema and congestion (incidence not specified); membranous tracheitis and focal pulmonary hemorrhage in one monkey At 72 hrs, no edema or congestion At 7 days, emphysema and atelectasis in one monkey; no findings in 2nd monkey At 30 days, emphysema and atelectasis in one monkey; extensive early pneumonia in 2nd monkey
2615	11	28,765	8 monkeys died within 24 hrs At 24 hrs, one monkey terminated exhibited bronchial and pulmonary damage, and visceral congestion At 29 days, last monkey died; exhibited similar lesions as above.

Striker et al., 1967a.

DATA SUMMARY - ADAMSITE (DM)

Animal Data

Monkeys

Effects of Exposure Concentration and Duration on Response Severity in Monkeys to Inhaled Adamsite (DM)			
Concentration (mg/m^3)	Duration (min)	Ct ($mg \cdot min/m^3$)	Effects
291	2	582	Modest hyperactivity during exposure, blinking. Slight pulmonary congestion with greater severity at 1 week and 30 days post exposure
291	10	2910	Modest hyperactivity during exposure, blinking. Focal pulmonary edema and bronchorrhea at 12 hrs; edema cleared at 24 hrs but bronchorrhea/bronchitis persisted to 30 days
272	20	5440	Modest hyperactivity during exposure, blinking, depression, vomiting. Focal pulmonary edema and bronchorrhea of greater severity than at 2910 $mg \cdot min/m^3$
330	40	13,200	Conjunctival congestion, depression, oral and nasal discharges, vomiting, dyspnea. Similar pathological findings as for 5440mg/m^3
99	2	198	Mild blinking. Pulmonary edema, congestion, bronchorrhea observed at 72 hrs was cleared at 1 week
108	12	1296	Blinking. Pulmonary edema, congestion, bronchorrhea persisted to 30 days
77	60	4620	Tearing, blinking, depression, rapid respiration, gasping, trace oral and nasal discharges. Labored breathing, pulmonary edema, congestion, bronchorrhea marked at 72 hrs but resolved at days 7 and 30

Striker et al. 1967b.

DATA SUMMARY - ADAMSITE (DM)

Animal Data

Monkeys

- 10-day exposure of monkeys (Owens et al., 1967):
  11,606 mg-min/m^3: 5 of 8 died
  17,302 mg-min/m^3: 8 of 8 died
- acute inhalation, monkeys (McNamara et al., 1969)
  25,085 mg-min/m^3 (214 mg/m^3, 117 min.): 6 of 6 died
  12,555 mg-min/m^3 (279 mg/m^3, 46 min.): 0 of 6 died

Dogs

- 30-min. exposure (Craighill and Folkoff, 1922)
  400-620 mg/m^3 results in death within 12 days
  650 mg/m^3 results in death within 48 hrs.
  110 mg/m^3 no deaths at 9 days
- 10-day exposure of dogs (Owens et al., 1967):
  11,606 mg-min/m^3: 1 of 8 died
  17,302 mg-min/m^3: 2 of 8 died
- acute inhalation, dogs (McNamara et al., 1969)
  9,064 mg-min/m^3 (206 mg/m^3, 44 min.): 6 of 6 died
  2,968 mg-min/m^3 (212 mg/m^3, 14 min.): 0 of 6 died

DATA SUMMARY - ADAMSITE (DM)

Animal Data

Rats

- LCt_{50} 3000 mg-min/m^3 (Gongwer et al., 1958)
- LCt_{50} 3700 mg-min/m^3 (Punte et al., 1958)
- LCt_{min} 1200 mg-min/m^3 (Gongwer et al., 1958)
- No lethality or pathology at 500 mg-min/m^3 (Punte et al., 1958)
- acute inhalation, rats (McNamara et al., 1969)
  12,555 mg-min/m^3 (279 mg/m^3, 45 min.): 1 of 20 died
  5,940 mg-min/m^3 (297 mg/m^3, 20 min.): 0 of 20 died

Guinea Pigs

- LCt_{50} 7,900 mg-min/m^3 (McNamara et al., 1969)

AEGL-3 DEVELOPMENT FOR ADAMSITE (DM)

- Key Studies: Striker et al., 1967a; McNamara et al., 1969

- Point-of Departure:
  - for 10-min AEGL-3:
    - severe pulmonary damage; emphysema-like condition and persistent pneumonia without lethality in monkeys following 5-min exposure to 1708 mg/m^3 (Striker et al., 1967a)
  - for 30-min, 1, 4, and 8-hr AEGL-3:
    - 279 mg/m^3 for 46 min was highest nonlethal exposure for monkeys (McNamara et al., 1969)

- Time Scaling:
  - n = 0.71 based upon data tolerance limits of human volunteers

AEGL-3 DEVELOPMENT FOR ADAMSITE (DM)

- Uncertainty Adjustment
  - 3 for individual variability
  - 10 for interspecies variability

AEGL-3 Values For Adamsite (DM)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3

AEGL-1 DEVELOPMENT FOR ADAMSITE (DM)

- **Key Studies:**
  - **Gongwer et al. (1958); Craighill and Folkoff, (1922); Lawson and Temple (1922)**

- **Point-of Departure:**
  tolerance limit (human volunteer subjects) for ocular and nasopharyngeal irritation
  - **20 mg/m^3 for 2 min (Gongwer et al., 1958)**
  - **0.14 mg/m^3 for 60 min (Craighill and Folkoff, 1922)**

- **Tolerance limit too severe for AEGL-1; therefore above POD reduced 3-fold:**
  - **6.7 mg/m^3 for 20 min (10-min and 30-min AEGL-1)**
  - **0.047 mg/m^3 for 60 min (1, 4, and 8-hr AEGL-1)**

- **Time Scaling:**
  - **n = 0.71 based upon data tolerance limits of human volunteers**

- **Uncertainty Adjustment:**
  - **3 for individual variability**

AEGL-1 Values For Adamsite (DM)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.23 mg/m^3	0.05 mg/m^3	0.02 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3

AEGL-2 DEVELOPMENT FOR ADAMSITE (DM)

- Key Study: Striker et al., 1967b

- Point-of Departure:
  - respiratory tract gross pathology in monkeys characterized by pulmonary edema, tracheal and bronchial damage which resolved within 1 month following exposure to 291 mg/m^3 for 10 min. or 77 mg/m^3 for 60 min.

- Time Scaling:
  - n = 0.71 based upon data tolerance limits of human volunteers

- Uncertainty Adjustment
  - 3 for individual variability
  - 10 for interspecies variability

AEGL-2 Values For Adamsite (DM)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3

AEGL-2 DEVELOPMENT FOR PHENYLDICHLOROARSINE (PD)

- Toxicity data were not available with which to develop AEGL-2 values for PD. Due to the quantitatively and qualitatively poor data base for PD, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended.

DATA SUMMARY - PHENYLDICHLOROARSINE (PD)

Human Experience

- Non verifiable lethality estimate (MLC_{50} of 2,600 mg-min/m^3) (Sullivan and Krieger, 1992)

- Non verifiable median incapacitating dose (ICt_{50} of 16 mg-min/m^3) (Sullivan and Krieger, 1992)

Animal Data

- Mouse MLC_{50} of 330 mg/m^3 (Skipper et al., 1942)
  - most deaths within 24 hrs; 10-day observation

AEGL-3 DEVELOPMENT FOR PHENYLDICHLOROARSINE (PD)

- **Key Study: Allen et al., 1922**

- **Point-of Departure:**
  - **10-min LC_{50} of 330 mg/m^3 in groups of 20 mice; 10-day observation**
  - **Lethality threshold estimated as 3-fold reduction of LC_{50} - 110 mg/m^3 (NRC, 2001)**

- **Time Scaling:**
  - **An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed**
  - **Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods.**
  - **Longer duration AEGL-3 values for ED are not recommended.**

- **Uncertainty Adjustment**
  - **3 for individual variability**
  - **10 for interspecies variability**

AEGL-1 DEVELOPMENT FOR PHENYLDICHLOROARSINE (PD)

- Data were not available with which to develop AEGL-1 values for PD and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for PD making extrapolation from DM or other chloroarsines tenuous and uncertain.

AEGL-1 DEVELOPMENT FOR ETHYLDICHLOROARSINE (ED)

- Data were not available with which to develop AEGL-1 values for ED and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for ED making extrapolation from DM or other chloroarsines tenuous and uncertain.

AEGL-2 DEVELOPMENT FOR ETHYLDICHLOROARSINE (ED)

- Toxicity data were not available with which to develop AEGL-2 values. Due to the quantitatively and qualitatively poor data base for ED, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended.

AEGL-3 DEVELOPMENT FOR PHENYLDICHLOROARSINE (PD)

- Modifying Factor
  - A modifying factor of 2 was applied to account for the limited data on PD; essentially only poorly described lethality studies were available.

AEGL-3 Values For Phenyldichloroarsine (PD)					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-3	**1.8 mg/m^3**	**0.61 mg/m^3**	**0.31 mg/m^3**	**NR**	**NR**

DATA SUMMARY - ETHYLDICHLOROARSINE (ED)

Human Experience

- Non verifiable median incapacitating dose (ICt_{50} of 5-10 mg-min/m^3) (Sullivan and Krieger, 1992)

Animal Data

- Mouse LCt_{50} of 1,555 mg-min/m^3 (Hutchens et al., 1943)
- Nonverifiable mouse LCt_{50} of 3,400 mg-min/m^3; no specific exposure terms (EATR, 1941)

DATA SUMMARY - METHYLDICHLOROARSINE (MD)

Human Experience

- Nonverifiable nasal irritation threshold of 0.8 mg/m^3 (Macy 1931)

Animal Data

- **Dog lethality study (Allen et al., 1922)**
  - **11-30 dogs/group; MD 98.5% purity**
  - **Exposure regimen:**
    - **846±90 mg/m^3 for 7. 5min**
    - **377±74 mg/m^3 for 15 min**
    - **160±38 mg/m^3 for 30 min**
    - **59±18 mg/m^3 for 60 min**
    - **33±4 mg/m^3 for 120 min**
  - **most deaths occurred 24-48 hrs post exposure**

DATA SUMMARY - METHYLDICHLOROARSINE (MD)

Animal Data

- **pathology indicated tracheobronchial/pulmonary damage as cause of death**
- **LC_{50} reported as:**
  - **815 mg/m^3 (7.5 min)**
  - **303 mg/m^3 (15 min)**
  - **125 mg/m^3 (30 min)**
  - **47 mg/m^3 (60 min)**
  - **31 mg/m^3 (120 min)**

AEGL-3 DEVELOPMENT FOR ETHYLDICHLOROARSINE (ED)

- Key Study: Hutchens et al., 1943
- Point-of Departure:
  - Ct of 1,555 mg-min/m^3 for 10-min exposures equivalent to an LC_{50} of 155.5 mg/m^3
  - Lethality threshold estimated as 3-fold reduction of LC_{50} - 51.8 mg/m^3 (NRC, 2001)
- Time Scaling:
  - An empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed
  - Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure period to the 30-minute and 60-minute AEGL-3 time periods.
  - Longer duration AEGL-3 values for ED are not recommended.
- Uncertainty Adjustment
  - 3 for individual variability
  - 10 for interspecies variability

AEGL-3 DEVELOPMENT FOR ETHYLDICHLOROARSINE (ED)

- Modifying Factor
  - A modifying factor of 2 was applied to account for the limited data on ED; essentially only poorly described lethality studies were available.

AEGL-3 Values For Ethyldichloroarsine (ED)					
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-3	**0.86 mg/m^3**	**0.29 mg/m^3**	**0.14 mg/m^3**	**NR**	**NR**

AEGL-3 DEVELOPMENT FOR METHYLDICHLOROARSINE (MD)

- Key Study: Allen et al. (1922)

- Point-of -Departure:
  - time-specific LC_{50} values for dogs
    - 7.5 min: 815 mg/m^3
    - 30 min: 125 mg/m^3
    - 60 min: 47 mg/m^3
    - 120 min: 31 mg/m^3
  - Lethality thresholds for these time periods were estimated as a 3-fold reduction of the reported LC_{50} values:
    - 271.6 mg/m^3 for 7.5 min (for development of 10-min AEGL-3)
    - 41.7 mg/m^3 for 30 min (for development of 30-min AEGL-3)
    - 15.7 mg/m^3 for 60 min (for development of 1-hr AEGL-3)
    - 10.3 mg/m^3 for 120 min (for development of 4-hr and 8-hr AEGL-3)

AEGL-3 DEVELOPMENT FOR METHYLDICHLOROARSINE (MD)

- Time Scaling:
  - $n = 0.82$ based upon dog lethality (Allen et al., 1922)

- Uncertainty Adjustment
  - 3 for individual variability
  - 10 for interspecies variability

AEGL-3 Values For Methyldichloroarsine (MD)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	6.4 mg/m^3	1.4 mg/m^3	0.52 mg/m^3	0.15 mg/m^3	0.06 mg/m^3

AEGL-1 DEVELOPMENT FOR METHYLDICHLOROARSINE (MD)

- Data were not available with which to develop AEGL-1 values for MD and, therefore, none are recommended. It is currently not possible to characterize the exposure-response curve for MD, thus making extrapolation from other chloroarsines tenuous and uncertain.

AEGL-2 DEVELOPMENT FOR METHYLDICHLOROARSINE (MD)

- Data consistent with AEGL-2 type effects were unavailable with which to develop AEGL-2 values for MD. Consistent with AEGL procedures and methodologies (NRC 2001), the AEGL-2 values for MD were estimated as one third of the AEGL-3 values.

AEGL-1 DEVELOPMENT FOR DIPHENYLCHLOROARSINE (DA)

- Data were not available with which to develop AEGL-1 values for DA and, therefore, none are recommended. Furthermore, data were unavailable with which to characterize the exposure-response curve for DA making extrapolation from DM or other chloroarsines tenuous and uncertain.

AEGL-2 DEVELOPMENT FOR DIPHENYLCHLOROARSINE (DA)

- Toxicity data were not available with which to develop AEGL-2 values. The lethality studies in dogs, rats, mice, rabbits, and cats did not characterize nonlethal toxic responses. Due to the quantitatively and qualitatively poor data base for DA, development of AEGL-2 values by extrapolation from AEGL-3 values is not recommended.

DATA SUMMARY - DIPHENYLCHLOROARSINE (DA)

Human Experience

- nasal irritation threshold of 1.5 mg/m^3 (Macy, 1931)
- throat irritation threshold of 2.5 mg/m^3 (Macy, 1931)

DATA SUMMARY - DIPHENYLCHLOROARSINE (DA)

Animal Data

- lethality data in multiple species (MMW, 1918)
  - no deaths among rats (4/group), rabbits (2/group), or cats (2-4/group) exposed to 236 mg/m^3 for 30 min or 118 mg/m^3 for 60 min
  - neither of 2 cats died following 15-min exposure to 8850 mg/m^3
  - one of 2 rats died following 30-min exposure to 8850 mg/m^3
- nonverifiable lethality estimates for mice
  - 10-min LC_{lo} of 298 mg/m^3 (cited by CWS, 1944)
  - 10-min LC_{50} of 690 mg/m^3 (EATR, 1933)
  - 10-min LC_{50} of 853 mg/m^3 (cited by CWS, 1944)
  - 10-min LC_{50} of 1300 mg/m^3 (cited by Kibler et al., 1942)

Summary/Relationship of AEGL Values (mg/m^3)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
Adamsite (DM)					
AEGL-1 (Nondisabling)	0.23 mg/m^3	0.05 mg/m^3	0.02 mg/m^3	0.0022 mg/m^3	0.00083 mg/m^3
AEGL-2 (Disabling)	9.7 mg/m^3	6.8 mg/m^3	2.6 mg/m^3	0.36 mg/m^3	0.14 mg/m^3
AEGL-3 (Lethal)	21 mg/m^3	17 mg/m^3	6.4 mg/m^3	0.91 mg/m^3	0.34 mg/m^3
Diphenylchloroarsine (DA)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-3 (Lethal)	5.7 mg/m^3	3.9 mg/m^3	2.0 mg/m^3	0.49 mg/m^3	0.25 mg/m^3
Ethyldichloroarsine (ED)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	NR[b]	NR[b]	NR[b]	NR[b]	NR[b]
AEGL-3 (Lethal)	0.86 mg/m^3	0.29 mg/m^3	0.14 mg/m^3	NR[c]	NR[c]
Methyldichloroarsine (MD)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	2.1 mg/m^3	0.47 mg/m^3	0.17 mg/m^3	0.05 mg/m^3	0.02 mg/m^3
AEGL-3 (Lethal)	6.4 mg/m^3	1.4 mg/m^3	0.52 mg/m^3	0.15 mg/m^3	0.06 mg/m^3
Phenyldichloroarsine (PD)					
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (Disabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-3 (Lethal)	1.8 mg/m^3	0.61 mg/m^3	0.31 mg/m^3	NR[c]	NR

NR: Not recommended; insuffucient data.

[a] Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

[b] Absence of an AEGL-2 does not imply that exposure below the AEGL-3 is without severe and possibly irreversible adverse effects.

[c] 10-minute experimental data point is insufficient to support extrapolation to 4-hour and 8-hour exposure durations.

AEGL-3 DEVELOPMENT FOR DIPHENYLCHLOROARSINE (DA)

- Key Study: MMW, 1918

- Point-of -Departure:
  - no lethality in rats, rabbits, or cats following 30-min exposure to 236 mg/m^3 or 60-min exposure to 118 mg/m^3
  - 30-min exposure to 295 mg/m resulted in the death of i of 2 rats while neither of two cats died following 15-min exposure to 590 mg/m^3 and neither of two rabbits died following exposure to 1180 mg/m^3

- Time Scaling:
  - An empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed
  - Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 60-min exposure period to the 4- and 8-hr AEGL-3 time periods, and an n of 3 was used to extrapolate from the 30-minute experimental period to the 10-min AEGL-3 exposure.

AEGL-3 DEVELOPMENT FOR DIPHENYLCHLOROARSINE (DA)

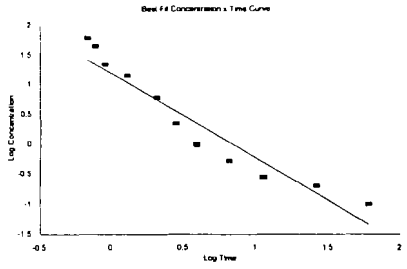
- Uncertainty Adjustment
  - 3 for individual variability
  - 10 for interspecies variability

- Modifying Factor
  - 2 for limited data

AEGL-3 Values For Diphenylchloroarsine (DA)					
Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	5.7 mg/m^3	3.9 mg/m^3	2.0 mg/m^3	0.49 mg/m^3	0.25 mg/m^3

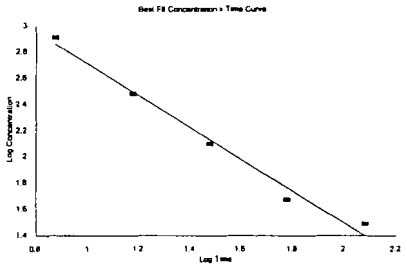
Adamsite (DM)
Human tolerance limits for adamsite (DM) based on average response of 1 to 6 volunteer subjects. (Lawson and Temple,1922; Craighill and Folkoff, 1922).

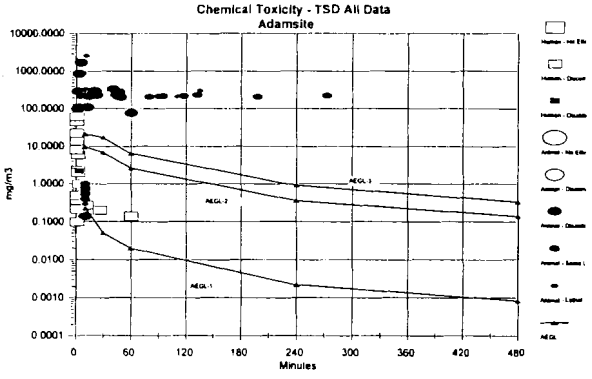
n =0.71 k =6.85

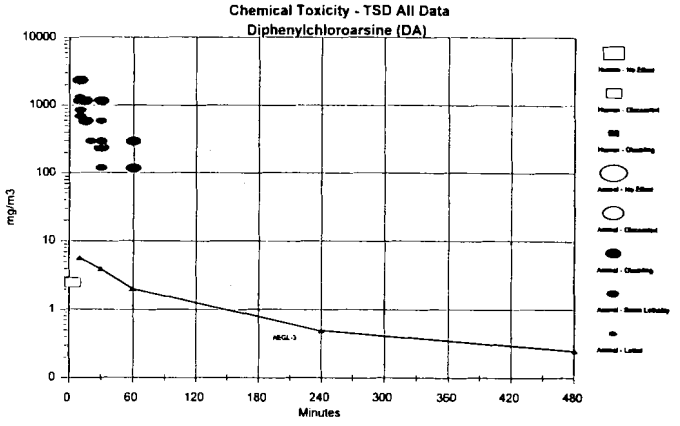


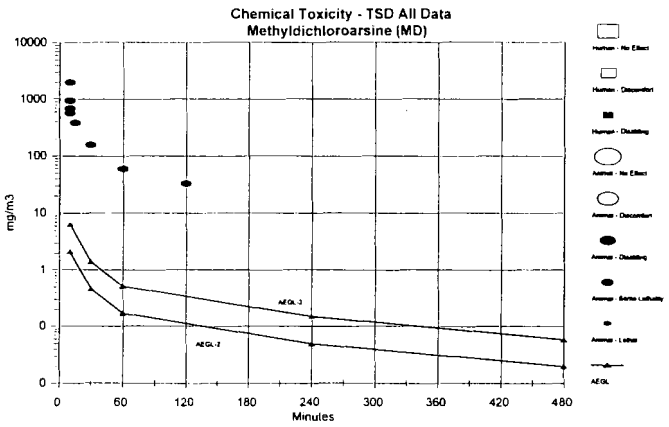
Methyldichloroarsine (MD)
Lethality in dogs (11-30 per group) exposed to MD (Allen et al., 1922)

n = 0.82
k = 1717.19








Chemical Toxicity - TSD All Data
Methyldichloroarsine (MD)
10000
1000
100
10
1
0
0
mg/m3
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CHLOROACETONE

NAC/AEGL-33
June 14-16, 2004
Voorburg, The Netherlands

ORNL Staff Scientist: Cheryl Bast
Chemical Manager: George Alexeeff
Chemical Reviewers: Steve Barbee and George Rusch

AEGL-1 VALUES: CHLOROACETONE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Data were insufficient for derivation of AEGL-1 values for chloroacetone.

AEGL-1 values for chloroacetone are Not Recommended (NR).

AEGL-2 VALUES: CHLOROACETONE				
10 minute	30 minute	1 hour	4 hour	8 hour
4.3 ppm	4.3 ppm	3.7 ppm	0.87 ppm	0.87 ppm

Endpoint:

30-min, 1-hr, and 4-hr:

Three-fold reduction of AEGL-3 values. Estimated threshold for the inability to escape.

10-min:

30-minute AEGL-2 value adopted as the 10-minute value because of the human case-report suggesting that exposure to 4.7 ppm causes immediate, severe irritation (Sargent et al., 1986); it would be inappropriate to exceed this value at any time point.

8-hr:

4-hour AEGL-2 value adopted as the 8-hour value; doing otherwise would drive the 8-hour AEGL-2 value approximately 2-fold below occupational standards.

Reference: **Arts and Zwart, 1987**

Time Scaling: **See AEGL-3 derivation.**

Uncertainty Factors:

Interspecies = 3 **See AEGL-3 justification.**

Intraspecies = 3 **See AEGL-3 justification.**

AEGL-3 VALUES: CHLOROACETONE				
10 minute	30 minute	1 hour	4 hour	8 hour
19 ppm	13 ppm	11 ppm	2.6 ppm	1.3 ppm

Species: Rat (5/sex/group)
Concentration: 105 ppm
Time: 1-hour
Endpoint: Estimated threshold for death (⅓ male rat LC_{50})
Reference: Arts and Zwart, 1987

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

Uncertainty Factors:
Interspecies = 3

Highly irritating chemical: Clinical signs caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species

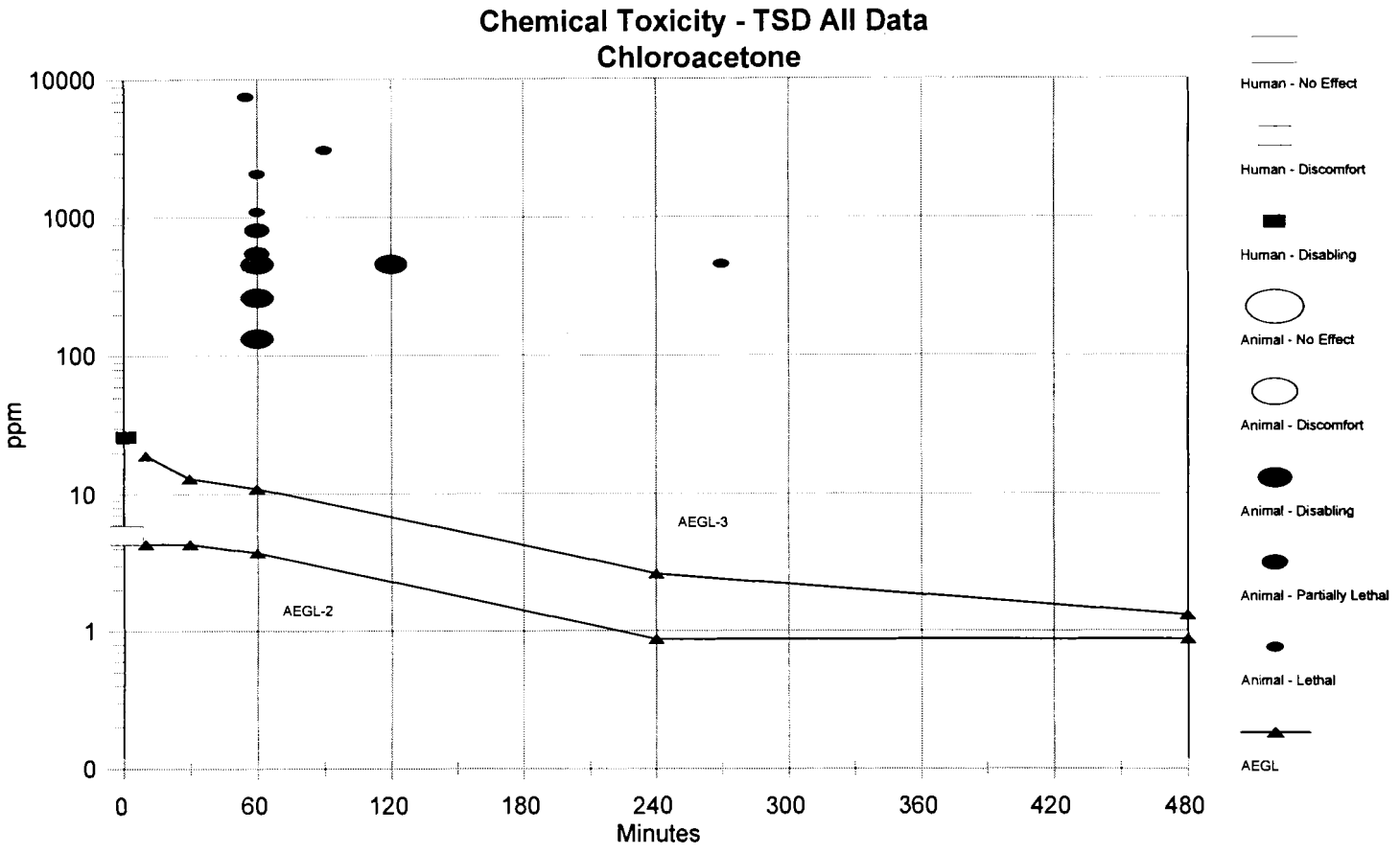
Little species variability with regard to lethality from oral and dermal exposure

rat oral LD_{50} values:	100-141 mg/kg
mouse oral LD_{50} values:	127-141 mg/kg
rabbit dermal LD_{50}:	141 mg/kg

1-hr LC_{50} of 500 ppm for male and female rats yields an approximate dose of 114 mg/kg, correlates well with the rat oral LD_{50} values (assuming 100% retention, 245 ml minute volume and a rat body weight of 250 g).

Intraspecies = 3 Highly irritating chemical: Clinical signs caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly among individuals

Point of departure was from most sensitive male rat



CHLOROACETONE					
Guideline	Exposure Duration				
	10-Min	30-Min	1-Hour	4-Hour	8-Hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.3 ppm	4.3 ppm	3.7 ppm	0.87 ppm	0.87 ppm
AEGL-3	19 ppm	13 ppm	11 ppm	2.6 ppm	1.3 ppm
ACGIH TLV-Ceiling					1ppm
Dutch MAC					1 ppm

ATTACHMENT 6

June 15, 2004

TSD Hexane

Chemical Manager: A. Feldt
Staff Scientist: M. Draaijer / P.M.J. Bos

Hexane: Uses

- Food processing (extraction solvent for vegetable oils)
- Cleaning agent (printing, textile, shoe-making, furniture)
- Glue (roofing, shoe and leather industry)

Hexane: Physical-chemical properties

- Molecular weight: 86.18
- Colorless liquid
- Water solubility: insoluble (9.5 mg/L)
- Boiling point: 69°C
- Odor: faint peculiar odor
- Flammability: highly flammable
- LEL: 1.1%

Hexane

- Technical grade n-Hexane
- Not:
  - commercial hexane (20-80% n-hexane; hexane isomers and related 6-C compounds)
  - mixed hexane
- Distal degenerative axonopathy (through 2,5-hexanedione) is not an issue for single exposure

Hexane: Case reports

- No relevant case reports available
- In case of abuse:
  - commercial hexane
  - repeated exposure
  - possible exposure to other substances

Hexane: Human data

- Experiments with volunteers
  - No subjective complaints in 4 Caucasian male volunteers exposed to 54 ppm for 2 h during light physical exercise
  - No complaints *reported* in several kinetic studies with exposures up to 200 ppm for 4 h.
- Occupational data
  - Co-exposures cannot be ruled out
  - Exposures generally not adequately reported
  - Usually focused on kinetics

Hexane: Human data

- No data on reproductive toxicity
- No data on genotoxicity
- No data on carcinogenicity

Hexane: Animal experiments

- Rat data:
  - most acute studies are focused on kinetics
- *Mouse data:*
  - most studies date from early 20th century
  - exposure under static conditions

Hexane: Animal data

Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	76,900 ppm	1 h	LC_{50}	Reported in Pryor *et al.* 1992
Rat	48,000 ppm	4 h	LC_{50}	Reported in Coon and Mitts 1982
Rat	48,280 ppm	2-10 h	No lethality	Rehder *et al.* 1973 (kinetic study)
Rat	10,000 ppm	0.5-6 h	No lethality	Raje and Rickert 1981 (kinetic study)
Rat	10,000 ppm	6 h	No lethality	Rao *et al.* 1982 (kinetic study)
Rat	86,227 ppm	30 min	No lethality	Raje *et al.* 1984 (kinetic study)
Rat	48,000 ppm 40,000 ppm	10 min/30 min, 3 bid, 5 d/w, 12 w 10 min/30 min, on a background of 4,000 ppm consumes, 5 bid, 5 d/w, 12 w	No lethality No lethality	Howd *et al.* 1982
Mouse	32,000 ppm 64,000 ppm	5 min <4.5 min	No lethality 100% lethality	Svirbely *et al.* 1974

Hexane: Animal data

Neurotoxicity (*Pryor et al. 1982*)

- Exposure of rats to 48,000 ppm (6 h/d, 5 d/w):
  - 10 weeks: 10 min/hour (6 exposure/day)
  - 8 weeks: 10 min/ 30 min (12 exposure/day)
  - 4 weeks: 10 min/15 min (24 exposure/day)
- No acute behavioral effects observed
  - (grip strength, conditioned avoidance response, motor activity)
  - "48,000 ppm did not cause myoclonic seizures in most of the rats"

Hexane: Animal data

- *Effects on brain enzymes* in rats exposed to 2000 - 8000 ppm for 8 hours
  - but no effects reported by Prior *et al.* 1982
- (Reversible) effects on testes in rats exposed to 5000 ppm for 14 hours
  - But no effects in rats exposed to 10,000 ppm for 6h/d; 5d/w for 13 w.
- (Electron microscopic) changes in lungs in rats exposed to 10,000 ppm for 8 hours.
  - ~~But no effects in rats exposed to 10,000 ppm for 6h/d; 5d/w~~ for 13 w.

Hexane: Animal data

- Old studies with mice dated from early 20th century with static exposures considered tio be of no relevance
- Groups of 4 mice exposed in a body plethysmograph for 5 min to 1000, 2000, 4000, 8000, 16,000, 32,000, 64,000 ppm (Swann et al. 1974)
  - 8000 ppm: no effects
  - 16,000 ppm: light anesthesia
  - 32,000 ppm: direct anesthesia
  - 64,000 ppm: death within 4.5 min

Hexane: Developmental effects

- Hexane (and metabolites) can cross the placenta after a single 6-hour exposure
- Pregnant rats exposed up to 1000 ppm for 23 h/d, 7d/w during and after gestation.
  - 4/8 dams gave birth at 1000 ppm
  - reduced bw and delay in brain development in newborns (recovery starting at 2 weeks after birth when exposed during gestation)

Hexane: Developmental effects

- Pregnant rats exposed to 1000 ppm for 6 h/d (Bus *et al.* 1979)
  - d 8-12, 12-16, 8-16 during gestation, sacrificed before birth
    no developmental toxicity observed
  - d 8-16 of gestation and follow-up for 7w after birth
    no effects at birth but transient growth reduction 3 w after birth
- Conclusion: no developmental effects following acute exposure (up to 8 h) to hexane

Hexane: Genotoxicity / carcinogenicity

- Genotoxicity
  - Predominantly negative results *in vitro*
  - Predominantly negative results *in vivo*
    few reversible effects on sperm
- Carcinogenicity
  - No data available with n-hexane, commercial hexane induced hepatocellular neoplasms in mice but not in rats

Hexane: Kinetic data

- Low alveolar retention (25-35%)
- Steady state hexane concentrations in blood reached within 30 min (exception: Bohlen et al. 1973, reporting 4-5 h)
- Species difference in distribution of hexane in blood
  - 94% in erythrocytes in rats (*in vivo* and *in vitro*)
  - 66% in erythrocytes in humans (*in vitro*)

Hexane: AEGL-1

- Predominant effect is CNS-depression
- No adequate human data
- Mice more susceptible than rats
  - Only one adequate mouse study by *Swann et al. (1974)*
  - 5 min exposures to a concentration range of 1000 - 64,000 ppm

Hexane: AEGL-1

- *Swann et al. (1974)*
  - no CNS-depression at 5 min exposure to 8000 ppm
  - most data point to rapid steady-state hexane concentrations (within 30 min)
    also: insoluble in water; analogous to propane, butane
  - effects are concentration-related: n=3
  - UF= 3
    effects considered to be due to hexane, therefore, no large differences in kinetics expected
    rather steep concentration-response curve thus small *inter*individual variation
    relative susceptible species used

Hexane: AEGL-1

- *Swann et al. (1974)*
  - point of departure: 5-min exposure to 8000 ppm
  - n=3 for time extrapolation to 30 min
  - flatlining from 30 min to 1-, 4- and 8-hour exposures because of steady-state reached within 30 min

AEGL-1 Values for Hexane				
10-minute	30-minute	1-hour	4-hour	8-hour
2100 ppm* (7400 mg/m³)	1500 ppm* (5300 mg/m³)	1500 ppm* (5300 mg/m³)	1500 ppm* (5300 mg/m³)	1500 ppm* (5300 mg/m³)

* The AEGL-1 value is higher than 10% of the lower explosive limit of hexane in air (LEL = 1.1 % (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

Hexane: AEGL-2

- Predominant effect is CNS-depression
- No adequate human data
- Rats:
  - no visible signs at 86,222 ppm for 20 min, ataxia after 25 min
  - myoclonic seizures at 48,000 ppm?
- Mice
  - Only one adequate mouse study by *Swann et al. (1974)*
    5 min exposures to 16,000 ppm caused light anesthesia, 32,000 ppm directly caused anesthesia

Hexane: AEGL-2

- *Swann et al. (1974)*
  - point of departure: 5-min exposure to 16,000 ppm
  - n=3 for time extrapolation to 30 min
  - flatlining from 30 min to 1-, 4- and 8-hour exposures because of steady-state reached within 30 min

AEGL-2 Values for Hexane				
10-minute	30-minute	1-hour	4-hour	8-hour
4200 ppm* (14,800 mg/m³)	2900 ppm* (10,200 mg/m³)	2900 ppm* (10,200 mg/m³)	2900 ppm* (10,200 mg/m³)	2900 ppm* (10,200 mg/m³)

* The AEGL-2 value is higher than 10% of the lower explosive limit of hexane in air (LEL = 1.1 % (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

Hexane: AEGL-3

- Predominant effect is CNS-depression
- No adequate human data
- Rats:
  - 1-h LC_{50} of 76,900 ppm and 4-h LC_{50} of 48,000 ppm cannot be evaluated
  - 4-h LC_{50} of 48,000 ppm appears to be in contradiction with other rat data (kinetics and repeat dose toxicity study)
  - mice appear to be more susceptible
- Mice
  - Only one adequate mouse study by *Swann et al. (1974)*
    no mortality after 5 min exposures to 32,000 ppm but 100% mortality at 64,000 ppm

Hexane: AEGL-3

- *Swann et al. (1974)*
  - point of departure: 5-min exposure to 32,000 ppm
  - n=3 for time extrapolation to 30 min
  - flatlining from 30 min to 1-, 4- and 8-hour exposures because of steady-state reached within 30 min

AEGL-3 Values for Hexane

10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	See below*

* The AEGL-3 value is higher than 50% of the lower explosive limit of hexane in air (LEL = 1.1 % (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.
The calculated 10-min AEGL-3 value is 8500 ppm (29,900 mg/m³). The respective calculated AEGL-3 values for 30-min, 1-hour, 4-hours, and 8-hours are similar: 5900 ppm (20,800 mg/m³).

Hexane: Summary of AEGL-values

Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	2100 ppm*	1500 ppm*	1500 ppm*	1500 ppm*	1500 ppm*
AEGL-2 (Disabling)	4200 ppm*	2900 ppm*	2900 ppm*	2900 ppm*	2900 ppm*
AEGL-3 (Lethal)	See below**	See below**	See below**	See below**	See below**

* The proposed value is higher than 10% of the lower explosive limit of hexane in air (LEL = 1.1 % (11,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.
** The proposed value are higher than 50% of the lower explosive limit of hexane in air (LEL = 1.1 % (11,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
The calculated 10-min AEGL-3 value is 8500 ppm (29,900 mg/m³). The respective calculated AEGL-3 values for 30-min, 1-hour, 4-hours, and 8-hours are similar: 5900 ppm (20,800 mg/m³)

15-6-2004

AEGL-derivation for DCM: Use of PBPK-modeling

rivm

National Institute for Public Health and the Environment

Research for man and environment

Introduction

- AEGL-derivation for DCM first presented in sept 2002
- Discussion on the use of PBPK-modeling:
  - background of the PBPK-model (description and validity)
  - validity of the model for high concentrations
  - verification with additional data from public literature
  - effects of GSTT polymorphism

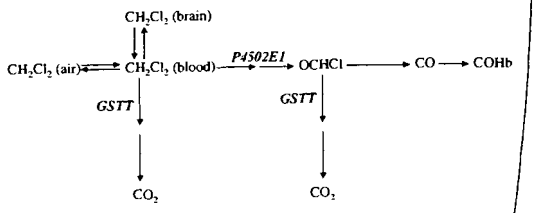
Introduction

- Reasons for PBPK-modeling for AEGL-derivation for DCM
- Construction of the model
  - validity and verification
- Conclusions on the PBPK-model
- Model application (AEGL-derivation)

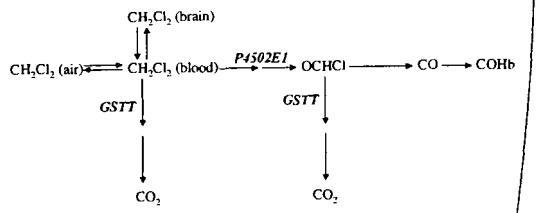
Reasons for PBPK-modeling

- Two different toxicity endpoints
  - CNS-depression, related to DCM concentration in brain
  - COHb-formation, via biotransformation to CO
- Switch of toxicity endpoint between 10 min and 8 hours of exposure
  - CNS-effects occur soon after onset of exposure
  - Peak levels of COHb can be reached hours after exposure
- No data available to estimate DCM concentration in air from predetermined COHb level
- PBPK-modeling is the only way for AEGL-derivation for DCM

Metabolism scheme of DCM

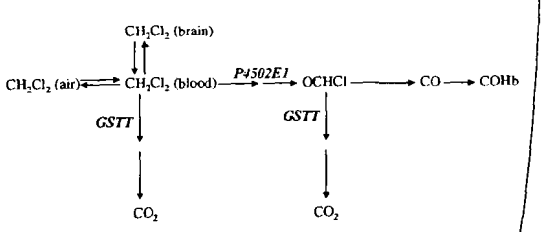


Metabolism scheme of DCM



- fast onset of effects (CNS-depression)

Metabolism scheme of DCM



- COHb formation, peaks after cessation of exposure
- pathway is saturable at approximately 300-500 ppm, both in rats and humans
- COHb levels for AEGL-derivation are predetermined for CO, there are no data available to calculate corresponding DCM concentrations in air!

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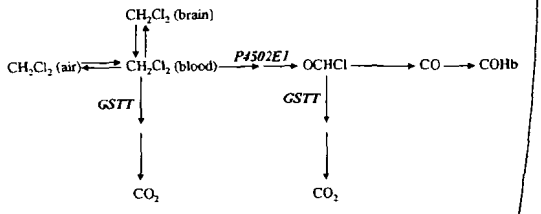
Metabolism scheme of DCM



- polymorphism (non- (20%), low-, and high-conjugators)
- becomes of importance above ca. 500 ppm
- GST-route related to carcinogenicity

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Reasons for PBPK-modeling

- CO-pathway saturable at about 300-500 ppm
  - lies within the extrapolation range
- Polymorphism of GSTT
  - higher CO formation in non-conjugators
- External air concentration of DCM is not the appropriate dose metric for extrapolation
  - extrapolation has to be based on predetermined internal dose metrics (DCM in brain versus COHb) within one model
- No data are available to estimate the DCM concentration in air from a predetermined COHb level

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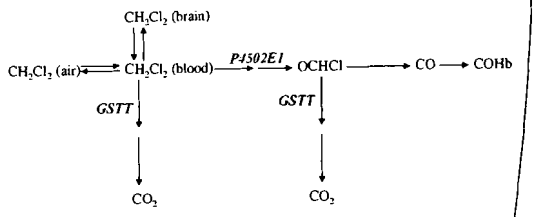
Construction of the model



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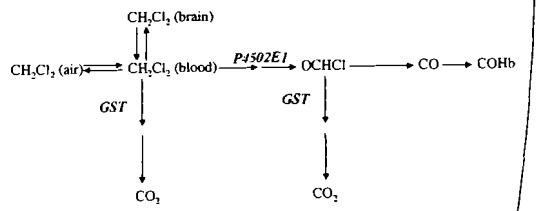
Construction of the model



- Basic model for DCM by *Andersen et al. 1987*
- Peer reviewed and used by US EPA for the calculation of the inhalation Unit Risk (IRIS-database)
- Extrapolation over several orders of magnitude (no GSTT-polymorphism)

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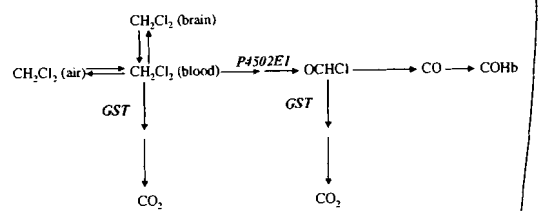
Construction of the model



- 1987-model extended with CFK-equation for COHb formation (CFK-equation used for AEGL-derivation for CO) *Andersen et al. 1991*

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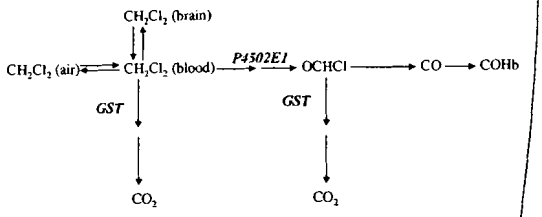
Construction of the model



- Andersen-model extended with a separate brain compartment by *Reitz et al. 1997*
- Peer reviewed and used by the ATSDR for the derivation of a 24-hour MRL based on DCM concentration in brain as dose metric

Construction of the model

- Five compartments incorporated
  - Fat
  - Liver
  - Brain
  - Slowly perfused tissues
  - Rapidly perfused tissues
- GSTT polymorphism
- Dose metrics
  - DCM concentration in brain } recalculated to air
  - COHb % } concentrations

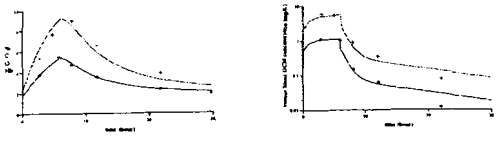
Construction of the model: *Summary*

- PBPK-modeling
  - Combination of components previously peer reviewed, accepted and used for risk assessment by different organizations
    Andersen et al. (1991): COHb formation
    Reitz et al. (1997): addition of brain compartment
  - DCM concentration in brain **and** COHb formation within one model
  - Development of specific algorithms to estimate the time-concentration relation for predetermined DCM concentrations in brain and predetermined peak COHb levels (from TSD on CO)

Human PBPK-model: reproducibility

- Andersen et al., 1991
  - *6 volunteers exposed for 6 hours to 100 or 350 ppm*
  - DCM in blood, exhaled air
  - CO in exhaled air
  - COHb

Human PBPK-model: reproducibility



Conclusion: Andersen et al. (1991) human model could be adequately reproduced

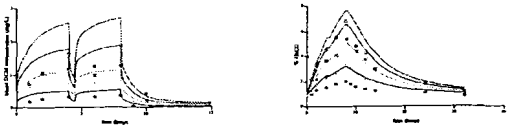
Human PBPK-model: verification

Application of the model to other populations

- Natural variation (physiology, kinetics)
  - Models cannot predict every individual
- Analytical errors
- Time-response curve of dose metric is of more importance than exact levels

Human PBPK-model: verification

- DiVincenco and Kaplan, 1981
  - 14 volunteers exposed for 7.5 hour to 50, 100, 150, 200 ppm



- difference of predicted vs. observed is at most 50%
- acceptable in view of general interindividual variation
- adequate prediction of the curves of the dose metrics

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Human PBPK-model: brain compartment

Reitz et al. 1997:

- Similar model was validated for methyl chloroform
  - predictions were in close agreement with measurements
- Simulation of brain concentration of DCM (human exposure to 300 ppm for 4 hours) could be reproduced
- Model was peer reviewed and accepted for DCM by the ATSDR for a purpose similar to AEGL-derivation

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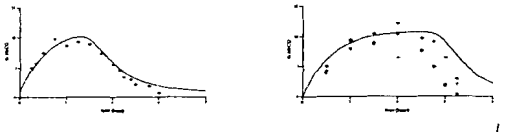
Rat PBPK-model: validity at high concentrations

Andersen et al., 1991: COHb levels

- left panel: groups of 3 rats exposed to 5159 ppm (0.5 h)
- right panel: three individual rats exposed to 1014 ppm (4 h)



Conclusion: Peak levels of COHb are adequately predicted at high exposure concentrations

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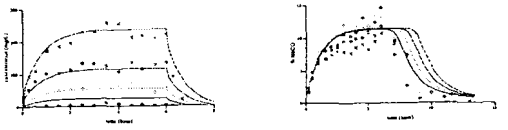
Rat PBPK-model: verification

- Green et al., 1986: demonstrates saturability
  - Groups of 3 rats (interim kills) exposed to 500, 1000, 2000, or 4000 ppm
  - left panel: DCM in blood; right panel: COHb

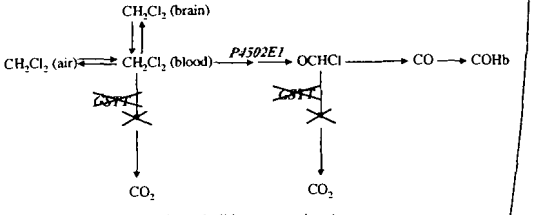


- Good prediction of DCM levels in blood
- Good prediction of saturation levels of COHb in rats

PBPK-model: Conclusions

- Most appropriate dose metrics (target tissue concentrations) are adequately predicted within one model:
  - good reproducibility of original models
  - adequate prediction of COHb and DCM in blood in both human and rat
- Kinetics are similar in humans and rats
  - adequate prediction at high concentrations
- Model is applicable for AEGL-derivation

Model application: *GSTT polymorphism*



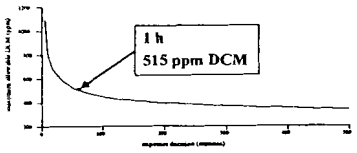
- GSTT-route was switched off for non-conjugators
- higher COHb formation

Model application for AEGL-derivation

- General parameter setting according to Andersen et al. (1991) and Reitz et al. (1997)
  - accepted by US EPA and ATSDR
- Predetermined COHb-levels adapted from TSD on CO
  - no AEGL-1 derived
  - AEGL-2: maximum of (additional) 4% COHb
  - AEGL-3: maximum of approximately (additional) 15% COHb

Model application: *CNS-effects*

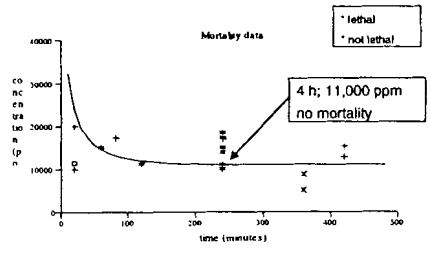
- Human data: 1 hour to 514 ppm DCM
  - brain concentration: 0.063 mM



Time-extrapolation based on DCM in brain as dose metric is possible

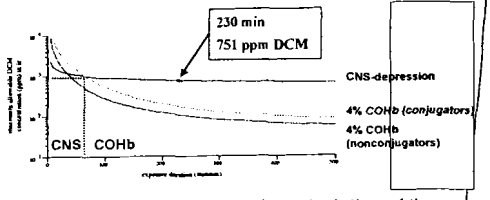
Model application: *animal mortality*

- + mouse; * rat; o rabbit; x guinea pig



Model application: *COHb and CNS-effects*

- Human data: 230 min to 751 ppm DCM
  - brain concentration: 0.137 mM; 4% COHb



Conclusion: Model is necessary for calculation of the intersection

Conclusions

- The DCM concentration in brain **and** the COHb level can be adequately predicted within one model
- Saturation of the CO-pathway and GSTT polymorphism can be adequately accounted for
- Time extrapolation based on the appropriate dose metrics is possible with the PBPK-model
  - calculation of the DCM concentration in air from a predetermined COHb level is possible **only** with a PBPK-model
- PBPK-model is essential for the calculation of the intersection of the time-curves for the two dose metrics

Acknowledgement

- M.J. Zeilmaker
- J.C.H. van Eijkeren

15-06-2004

TSD Methylene chloride

Chemical Manager : R. Benson
Staff Scientist: P.M.J. Bos

rivm

Research for man and environment

Model application: *AEGL-1*

No AEGL-1 for CO

CNS-depression

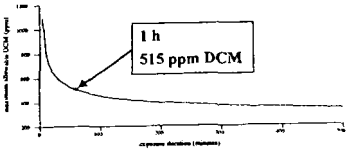
- Point of departure: Stewart et al (1972)
  - 1-h exposure to 515 ppm (n=8)
    no complaints
  - ***1-h exposure to 514 ppm***, 1-h exposure to 868 ppm (n=3)
    light-headedness and altered VER during the second hour
  - 2-h exposure to 986 ppm (n=3)
    no eye, nose, or throat irritation
    light-headedness (2/3); difficulties to enunciate (1/3) after 1 h; altered VER

AEGL-1 derivation

- CNS-effects
  - NOAEL: 1-h exposure to 515 ppm *(Stewart et al. 1972)*
  - effects related to DCM in brain (0.063 mM) and not to CO
  - no interspecies UF
  - intraspecies UF = 3
    no great variation between individuals

Model application: *AEGL-1*

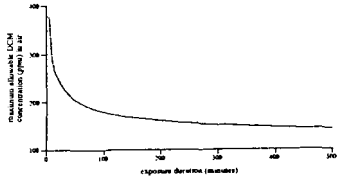
- Human data: 1 hour to 514 ppm DCM
  - brain concentration: 0.063 mM



rivm

Model application: *AEGL-1*

- Human data: 1 hour to 514 ppm DCM
  - UF=3 ⟶ brain concentration: 0.021 mM



rivm

AEGL-1 derivation

AEGL-1 Values for methylene chloride				
10-minute	30-minute	1-hour	4-hour	8-hour
390 ppm (1024 mg/m³)	230 ppm (812 mg/m³)	200 ppm (706 mg/m³)	*160 ppm (565 mg/m³)*	*140 ppm (495 mg/m³)*

rivm

AEGL-2: Human experiments

- Putz et al (1979)
  - exposure for 4 h to 195 ppm (n=12); main endpoints are AVT and response time
  - *some effects after 2 h of exposure, but sub AEGL-2 effects*
- Gamberale et al (1975)
  - subsequent 30-min exposures to 250, 500, 750, 1000 ppm
  - no effects on performance; subjective well-being rather 'improved'

AEGL-2: Human experiments

- Winneke and coworkers
  - exposure: 317, 470, and 751 ppm up to 230 min
  - endpoints: Auditory Vigilance Test, Critical Flicker *Frequency*
  - "something is happening" but no clear consistent results
  - effects are considered not to impair escape and therefore sub AEGL-2 effects

AEGL-2 derivation

- CNS-effects
  - 230 min to 751 ppm as a conservative NOAEL *(Winneke, 1974)*
  - related to CNS concentration in the brain
- COHb-related effects
  - no data for DCM
  - compliance with TSD for carbon monoxide:
    additional COHb of 4% (based on a reduced time until onset of angina during physical exertion in patients with coronary heart disease)

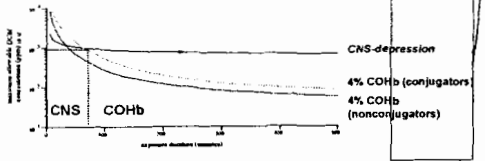
AEGL-2 derivation

- CNS-effects
  - Starting point: NOAEL at 230 min exposure to 751 ppm *(Winneke, 1974)*
  - DCM concentration in brain: 0.137 mM
  - no interspecies UF
  - intraspecies UF = 1
    - effects studied are sub AEGL-2 effects
    - mechanism of action will not vary greatly between individuals
    - intraspecies UF >1 will lead to unrealistic AEGL-2 values for CNS effects
- COHb level
  - 4% in compliance with AEGL-2 for carbon monoxide

rivm

AEGL-2 derivation

- Human data: 230 min to 751 ppm DCM
  - Dose metrics:
    brain concentration: 0.137 mM;
    4% COHb



rivm

AEGL-2 derivation

AEGL-2 Values for methylene chloride

Endpoint	10-minute	30-minute	1-hour	4-hour	8-hour
CNS-effects	1700 ppm	1200 ppm	1000 ppm	740 ppm	650 ppm
COHb (conj)	8400 ppm	2600 ppm	1100 ppm	160 ppm	85 ppm
COHb (non-conj)	4600 ppm	1400 ppm	560 ppm	100 ppm	60 ppm

rivm

AEGL-2: Human data

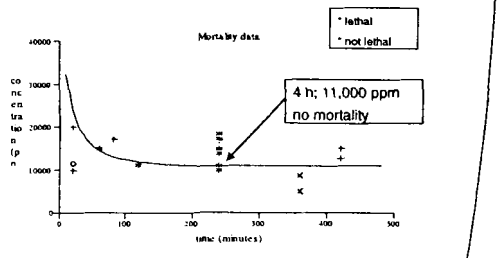
- Bicycle ergometer
  - 2 h to 500 ppm; up to 150 W
  - 1 h to 750 ppm; 50 W
- Occupational data (*Moynihan-Fradkin, 2001*)
  - 8-min TWA: 89-143 ppm; 41-969 ppm
  - 15-min TWA: 170-240 ppm; 140-1700 ppm
  - Effects reported: headaches (dermatitis, skin cracking), apparently no functional impairment

AEGL-3 derivation

- No adequate human data on mortality related to CNS-depression
- Compliance with TSD for carbon monoxide
  - no life-threatening symptoms at 40-56% COHb in healthy subjects
  - intraspecies UF of 3 used at corresponding CO concentrations
  - final AEGL-3 CO concentrations in air correspond to approximately 15% COHb

AEGL-3 derivation: *animal mortality*

- + mouse; * rat; o rabbit; x guinea pig



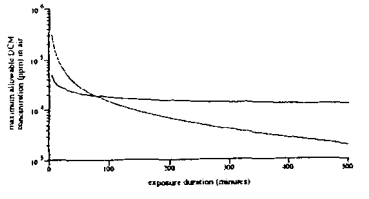
AEGL-3 derivation

- CNS-related mortality
  - starting point: 4-h exposure to 11,000 ppm in rats *(Haskell Laboratory, 1982)*
  - DCM concentration in rat brain: 3.01 mM
  - interspecies UF = 1
    - susceptibility between species is small
    - human PBPK-model is used
  - intraspecies UF = 3
    - mechanism of action (CNS-depressing effects) will not vary greatly between individuals
- COHb level
  - 15% in compliance with AEGL-3 for carbon monoxide

rivm

Model application: *AEGL-3*

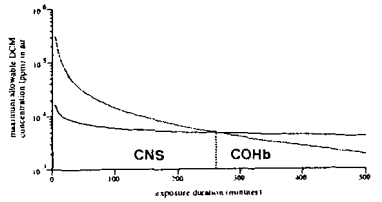
- Rat data: 240 min to 11,000 ppm
  - rat brain concentration: 3.01 mM



rivm

Model application: *AEGL-3*

- Rat data: 240 min to 11,000 ppm
  - human brain concentration: 1.0 mM



rivm

AEGL-3 derivation

AEGL-3 Values for methylene chloride					
Endpoint	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
CNS-effects	12,100 ppm	8500 ppm	6900 ppm	4900 ppm	4200 ppm
COHb (conj)	--	--	--	--	--
COHb (non-conj)	155,000 ppm	52,000 ppm	25,000 ppm	5300 ppm	2100 ppm

Summary of AEGL values

Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	290 ppm	230 ppm	200 ppm	NR	NR
AEGL-2 (Disabling)	1700 ppm	1200 ppm	1000 ppm	160 ppm	90 ppm
Non-conjugators			*360 ppm*	*100 ppm*	*60 ppm*
AEGL-3 (Lethal)	12,100 ppm	8500 ppm	6900 ppm	4900 ppm	4200 ppm
Non-conjugators					*2100 ppm*

NAC-AEGL Meeting

Sulfuric acid, sulfurtrioxide, and oleum

June 2004

Sulfuric acid, sulfurtrioxide, and oleum

- H_2SO_4 - SO_3
- oleum: a mixture of H_2SO_4 and SO_3, usually between 10-70% SO_3; fuming sulfuric acid
- SO_3 in ambient air reacts rapidly with water to form sulfuric acid mist
- Any residual inhaled SO_3 reacts instantly with moist air in the respiratory tract or ultimately with the mucous membranes
- Thus, for accidents with SO_3 or oleum, H_2SO_4 is the relevant exposure agent
- The Committee concluded in December 2003 that H_2SO_4, SO_3, and oleum are discussed in one TSD and AEGL-values are established only for sulfuric acid mist

Sulfuric acid - chemical and physical properties, use and production

- Strong acid (pK_a <0 and 1.92)
- Corrosive
- Colorless oily liquid
- Odor threshold 1 mg/m^3
- Very hygroscopic - formation of mist
- Exposure to aerosols
- Most produced chemical (1.7*10^8 m-tons)
- Fertilizer production (60%), pickling, batteries

Toxicological database for H_2SO_4

HUMAN DATA

- Some case studies in humans
- Many controlled human volunteers studies with in total more than 1000 volunteers
- In addition 15 occupational / epidemiologic studies

ANIMAL DATA

- Non-lethal tox: dozens of guinea pig studies, much less studies with other animals (monkey, dog, rat, mouse, hamster, rabbit, donkey, goat, sheep)
- Lethal tox: monkey, cat, rat, mouse, rabbit, guinea pig

Human data

LETHALITY

- One case report of a suicide with orally ingested sulfuric acid. Not relevant for AEGL.

NON-LETHAL TOX: CASE REPORTS

- Five case studies with accidental exposure. Main effects were symptoms of respiratory irritation, impaired lung function, and lung damage, which was reversible in most cases. No exposure estimates were available so these data cannot be used for AEGL.

Human data - continued

NON-LETHAL TOX: EXPERIMENTAL STUDIES

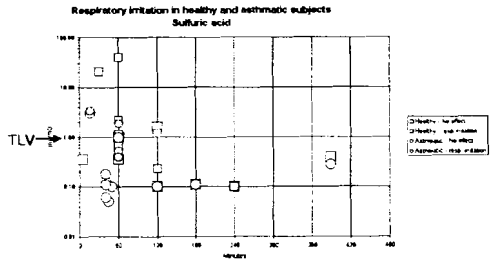
- Many studies (TSD table 4, p. 5-20) with more than 1000 volunteers in total
- Asthmatic and healthy volunteers
- Children - adults - seniors
- Exposure 0.01 - 3.37 mg/m^3 [20.8 and 39.4 mg/m^3]
- Duration 5 min - 6.5 hours
- Varying particle sizes
- Varying exposure methods (chamber, mouthpiece, ...) with and without exercise

- Increased sensitivity: depleted oral ammonia, no medication

Human data - continued

- MAIN EFFECTS VOLUNTEER STUDIES
- Respiratory irritation (most sensitive effect)
  - cough, throat irritation, chest tightness, burning sensations in nose and chest
    => All at least notable discomfort
- Impaired lung function
  - SR_{aw}, FEV_1, FVC
    => ΔSR_{aw} 100% still not biologically significant
    => ΔFEV_1 20% threshold for notable discomfort
- Mucociliary clearance
  - Increased or decreased, at levels without any symptoms, questionable significance for AEGL

Human data - respiratory irritation



More than 600 volunteers

Human data - occupational studies

- 12 studies
- Occupational exposure concentrations up to 1.7 mg/m^3 (personal samples) or 35 mg/m^3 (area samples)
- up to 35 mg/m^3: dental erosion, chronic bronchitis, slight decrease in FEV_1
- up to 1.7 mg/m^3: dental erosion, but no symptoms or lung function changes
- up to 1.5 mg/m^3: changes in nasal mucosa

Human data - continued

- OTHER EFFECTS
- No human data on neurotox, reprotox, or genotox
- Several epidemiological studies, revealing no, weak, or moderate associations between sulfuric acid exposure and cancer
- IARC 1992: occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans

Animal data

THE GUINEA PIG

- Much more sensitive than other species, despite lower total deposition
- Much lower LC_{50}'s due to reflex airway constriction
- Non-lethal effects are also related to these reflexes
- Using guinea pig data on toxicity would lead to very low and unrealistic AEGLs in view of human data
- As discussed in December, the guinea pig data are unsuitable for AEGL development

Animal data

ACUTE LETHALITY

- Runckle & Hahn very useful; time and concentration

RAT: 8 animals per group
mortality

concentration in mg/m3	exposure time in hours 1	2	4	8
240	0 / 8	0 / 8	0 / 8	0 / 8
470	1 / 8	0 / 8	5 / 8	7 / 8
730	1 / 8	3 / 8	5 / 8	7 / 8
800	0 / 8	5 / 8	6 / 8	7 / 8
1090	0 / 8	3 / 8	5 / 8	
1080			7 / 8	8 / 8

MOUSE: 10-12 animals per group
mortality

concentration in mg/m3	exposure time in hours 1	2	4	8
240	0 / 10	0 / 10	0 / 10	0 / 10
550	0 / 10	0 / 10	2 / 10	4 / 10
730	3 / 10	1 / 10	3 / 10	7 / 10
1040	5 / 12	8 / 14	11 / 14	

Animal data - continued

ACUTE LETHALITY - Continued

- High concentrations caused no mortality in:
  - rabbits (up to 839 mg/m³; 3 * 7 hours; follow-up >9 d)
  - one cat (461 mg/m³; 7 hours; sacrifice 48 h after exp.)
  - two monkeys (502 mg/m³; 7 days; follow-up not specified)

Animal data - continued

NON-LETHAL TOXICITY

- Similar effects as in humans
  - signs of respiratory irritation
  - effects on lung function
  - lung damage (hemorrhage, reversible squamous metaplasia, ulceration, loss of cilia, atelectasis, focal emphysema).

    No histological effects in respiratory tract of monkeys after a 7 days exposure to 502 mg/m³
- Not embryotoxic, fetotoxic, or teratogenic in mice and rabbits
- No *in vivo* genotox data, not tumorogenic in ~~hamsters, small increase in resp.tract tumors in rats~~ (intratracheal installation)

Special considerations

MECHANISM OF TOXICITY

- Direct local irritation of the respiratory tract
- Titratable acidity (amount of dissociated H^+ ions) determines the effect size

DEFENSE MECHANISMS

- Decreasing the reactions of H^+ with epithelial lung cells by:
  - mucus pH
  - high molecular fractions in mucus (buffering capacity)
  - ~~respiratory ammonia~~

Neutralisation by respiratory ammonia

- Gaseous ammonia in breath (10-3170 µg/m^3) neutralises H_2SO_4 to ammoniumsulfate or ammoniumbisulfate
- Nearly all controlled human volunteer studies used pre-exposure gargling with citric acid to deplete oral/respiratory ammonia
- An acidic oral rinse (pH 2.5) gives a 90% reduction of ammonia and may return to 50% of baseline levels after 1 h
- Respiratory effects can be enhanced by a factor 2 when subjects gargled citrus juice (Utell; MMAD 0.8 µm)

Asthmatics

IMPAIRED DEFENSE

- (Some) asthmatic people have
  - acidic mucus
  - mucus with low protein concentration
  - less ammonia production
- Thus, asthmatic people represent a sensitive subpopulation
- Fortunately, many data with asthmatic volunteers are available

Special considerations - deposition

- Sulfuric acid is hygroscopic
- Due to high humidity in the resp. tract particles will grow following inhalation until they reach the upper parts of the lung
- Growth of particles will change amounts and sites of deposition
- Growth and deposition will be different for different animal species and humans
- Extrapolation of observed toxicity of sulfuric acid in animal models to the human situation will be even more difficult due to differences in growth and deposition

=> Use human data whenever possible!

AEGL-1

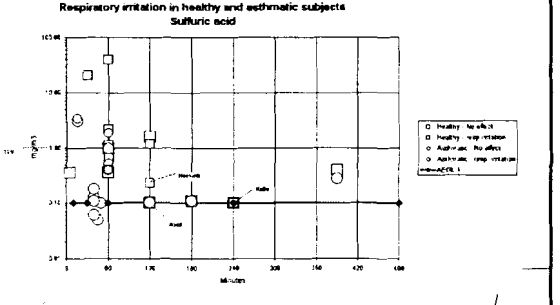
- *Symptoms of respiratory irritation most sensitive effect* (volunteer studies)
- 610 volunteers tested for irritation
  - incl.: asthmatic - young - adult - senior - exercise
  - increased sensitivity: acid oral rinse - withholding medication
- Kulle *et al.* 1982: 1/12 healthy volunteers "mild throat irritation" at 0.1 mg/m³
  - method not reported
  - *mild ≠ notable*
  - no irritation in other recent and well-performed studies involving 133 healthy/asthmatic volunteers at a similar dose

~~=> *this observation will not be used as a basis for AEGL-1*~~

AEGL-1

- Horvath *et al.* 1982: dose-dependent irritation from 0.23 mg/m³ onwards (120 min) in healthy exercising male volunteers
- Avol *et al.* 1979 provides a no-effect-level of 0.1 mg/m³ in exercising asthmatics at the same exposure duration
- The study of Avol can be used as point of departure for AEGL-1
  - healthy and asthmatic volunteers
  - withholding inhaled medications
  - intermittent bicycle exercise at 150-300 kg/min

AEGL-1



AEGL-1

- Flat-line across the AEGL timepoints because irritant effects do not vary greatly over time

AEGL-2

HUMAN DATA

- Linn *et al.* 1989: termination of exposure in 4/19 subjects at 2 mg/m^3 for 60 minutes
  - Sub-AEGL-2 effect above which impaired ability to escape might start
  - asthmatics who were withheld medication and gargled citric acid
  - intermittent exercise at 40-45 L/min
  - termination at second or third exercise i.e. 20-30 or 40-50 minutes

AEGL-2

- ANIMAL DATA
- No clear irreversible effects
- Serious health effects were (threshold in mg/m^3):
  - edema in rabbits (87) and mice (190)
  - hemorrhages in rabbits and rats (218)
  - desquamation bronchiolar epithelial cells in rabbits (218)
  - atelectasis and emphysema in rabbits (416)
  - larynx ulcers in rabbits (416), rats (96), and mice (140)
  - partly reversible larynx histopath in rats (5.52; 28 days)
- *NO* serious effects in monkeys (502; 7 days)
- Overall, no severe effects up to 60 mg/m^3 for up to 8 hours

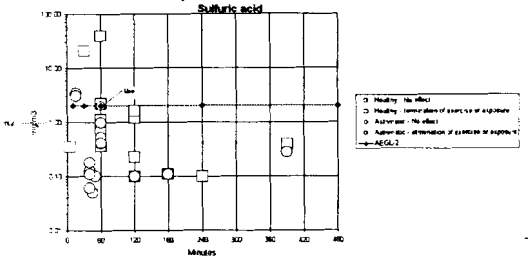
AEGL-2

- Human data are preferred above animal data, in particular when the different deposition of (hygroscopic) particles is considered
- The study of Linn *et al* can be used as point of departure for AEGL-2
- sub-AEGL-2 effect: no modifying factor
- very sensitive subpopulation: no safety factor
- resulting AEGL-2 value of 2 mg/m^3 is very conservative considering the reported occupational exposure concentrations

AEGL-2

Termination of exposure due to lung function and severe symptoms in healthy and asthmatic subjects

Sulfuric acid



AEGL-2

- Flat-line across the AEGL timepoints because irritant effects do not vary greatly over time

AEGL-3: Probit analysis

Exposure duration	RATS		MICE	
	LC_{01} (mg/m³)	95% confidence limits (mg/m³)	LC_{01} (mg/m³)	95% confidence limits (mg/m³)
10 minutes	1751	897 – 3620	796	475 – 1158
30 minutes	740	436 – 1132	592	379 – 770
1 hour	430	252 – 595	491	319 – 613
4 hours	145	63.8 – 217	338	206 – 426
8 hours	84.0	29.7 – 142	280	160 – 368

Modeling both concentrations and time

- Rat:
  - input data steep and irregular response vs concentration
  - result not very consistent with input data and other rat data
- Mouse: useful data, LC_{01} will be used for AEGL-3

AEGL-3

- LC_{01} values from probit analysis of the mouse data from Runckle and Hahn
- No interspecies UF because:
  - mice are more sensitive than rats and rabbits
  - monkeys did not die and showed no serious effects up to 502 mg/m³ for 7 days
  - occupational concentrations up to 35 mg/m³ were tolerated during workshifts without severe acute effects
- Intraspecies UF of 3 is used for variation in sensitivity among humans

AEGL-3

10 min 30 min 1h 4-h 8-h

265 197 164 113

mg/m³

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: PHENOL (CORRECTION OF CALCULATION ERROR) **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	29,(~~*~~)	29,( )	23,( )	15,( )	12,( )
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: Rodgers Second by: Kim

AEGL 3 Motion by: _____ Second by: _____

LOA Motion by: _____ Second by: _____

Approved by Chair: [signature] DFO: Paul S Tobin Date: 6/14/04

Appendix B

NAC/AEGL M.M.
4/19/04 - 4/21/04
APPROVAL OF MINUTES

NAC/AEGL Meeting 33: June 14-16, 2004

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

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

Chemical Manager: **Staff Scientist:**

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

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	✓			
Glenn Leach	✓			
John Morawetz	A			
Richard Niemeier	✓			
Marinelle Payton	A			
Susan Ripple	✓			
George Rodgers	✓			
Marc Ruijten	✓			
George Rusch, Chair	✓			
Robert Snyder	✓			
Richard Thomas	✓			
George Woodall	✓			
TALLY	16/16			
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:** R. Niemeier **Second by:** N. Kim
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/14/04

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

April 19-21, 2004

Draft Meeting-32 Highlights

U.S. Department of Labor, Room C5515
200 Constitution Avenue
Washington, DC 20210

INTRODUCTION

Chairman George Rusch welcomed the committee, thanked Surender Ahir for the meeting arrangements, and introduced guests. Guests included Dr. Harald Müllerschön, Röhm GmbH & Co., Germany; Dr. Tessa Serex of the Great Lakes Chemical Corporation, USA; Kerry Ketcheson, Environment Canada; Dr. Alexey Potekhin of Saint-Petersburg State University, Russia, and Dr. Myra Weiner of the FMC Corporation, USA. Dr. Iris Camacho, a new hire on the USEPA OPPT Risk Assessment Division technical staff was also present. Designated Federal Officer Paul Tobin explained membership renewal, stating that some members would be serving for more than the usual six years. New memberships are for 1, 2, or 3 years. Consideration for renewal involved keeping/rotating the state memberships and involvement with the chemicals in progress.

The draft NAC/AEGL-31 meeting highlights were reviewed. Two editorial corrections were suggested and have been incorporated into the highlights. A motion was made by Richard Thomas and seconded by John Hinz to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-30 meeting highlights is attached (Appendix A).

The highlights of the NAC/AEGL-32 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-32 Agenda.

FEDERAL REGISTER NOTICES

The 15 chemicals submitted for comment to the *Federal Register* have not been published, and therefore, no public comments were received. In order to expedite raising the status of chemicals from proposed to interim and moving them on to the National Academy of Sciences, Paul Tobin suggested that chemicals with no public comments after the 30-day comment period automatically be raised to interim. These chemicals would not be addressed at the next meeting, but a notice

would be sent to NAC members regarding the proposed status change. John Morawetz suggested an overall 45-day waiting period for the status change. John Hinz moved to accept the 45-day period with a notice to NAC members at the end of the 30-day public comment period. The motion was seconded by George Woodall. The motion passed unanimously with a show of hands.

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

Comments from the *Federal Register Notice* of July 18, 2003, on the proposed AEGL values for bromine were reviewed and discussed by Sylvia Talmage (Attachment 3). Comments were received from Toxicology Excellence for Risk Assessment (TERA) and the American Chemistry Council (ACC). TERA commented on use of categorical regression for development of values, the desirability of a full translation of the Rupp and Henschler (1967) paper (which they provided), reconsideration of setting the bromine values based on chlorine, and encouraging industry to conduct some simple animal experiments with bromine. The ACC suggested that the present bromine values are not accurate or useful. They questioned the use of time-scaling for the AEGL-1, the setting of values below the detection and odor thresholds, the accuracy of the Rupp and Henschler study, and the endpoint for the AEGL-2. They also suggested using chlorine as a model for bromine values. Tessa Serex of the Great Lakes Chemical Corporation explained why industry did not wish to conduct toxicity experiments with bromine. Sylvia Talmage presented new bromine values based on the known relationship of the irritancy and toxicity of bromine to chlorine. In the absence of additional data, the NAC decided the draft values were appropriate. A motion was made by Ernie Falke and seconded by Bob Benson to raise the bromine values to interim. The motion passed by a show of hands.

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

Comments from the National Research Council, Committee on Toxicology, Subcommittee on AEGLs (COT/AEGL) on four interim chemicals were discussed. Methanol and phenol were reviewed by the COT/AEGL Subcommittee at its January 27-29, 2003 meeting. Comments were published in the Ninth Interim Report, July, 2003. Boron trifluoride and chlorine trifluoride were reviewed by the COT/AEGL Subcommittee at its July 21-23, 2003 meeting. Comments were published in the Tenth Interim Report, January 2004.

Methanol (CAS No. 67-56-1)

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

Peter Griem discussed the COT/AEGL's comments, noting that comments on methanol and phenol were conflicting (Attachment 4). The COT/AEGL considered the interim AEGL-1 values for methanol too conservative and recommended against using the pharmacokinetic study of Batterman et al. (1998) as the key study and suggested using a validated model instead. They suggested a "weight of evidence" approach. Peter suggested retaining the Batterman et al. (1998) study as the key study, but adding support from three occupational monitoring studies (NIOSH 1980; Frederick et al. 1984; Kawai et al. 1991). Ernie Falke moved and Richard Thomas seconded the motion to use this approach. The AEGL-1 values would remain the same. Documentation from the Batterman et al. authors regarding a survey of symptoms and informed consent would be requested. The motion carried (YES:18; NO: 2; ABSTAIN: 0) (Appendix B).

For the AEGL-2, the COT/AEGL rejected use of the mouse developmental toxicity studies of Rogers et al. (1993; 1997) because the toxicokinetics and metabolism of methanol are too different in mice and humans to extrapolate findings from one species to the other. The COT/AEGL suggested selection of a blood methanol level of 150-200 mg/L which is associated with modest, reversible CNS depression. The NAC decided to stay with the present study. It was suggested that Peter present both the Perkins and Bouchard models to the COT (with Perkins taking precedent). It was moved by John Hinz and seconded by Bob Snyder that the present values be retained. The motion passed with a unanimous show of hands.

Comments on the AEGL-3 values from individual COT/AEGL reviewers appeared to be conflicting, i.e., the NAC used a reasonable approach (acute lethal effects in humans after oral ingestion) vs a suggestion to use blood methanol of 300-400 mg/L as a starting point and then to use the pharmacokinetic model for time extrapolation. It was also suggested that blood formate rather than methanol be used as a dosimeter for species and time extrapolations. Peter pointed out that the PBPK models of Perkins et al. (1995) and Bouchard et al. (2001) yield similar values. The Bouchard model calculates blood levels for the respective methanol values. The present AEGL-3 values are based on a clinical treatment level of >500 mg/L (American Academy of Clinical Toxicology 2002). Based on the steep dose-response curve, a LOEL to NOEL factor of 2 was originally used to approach a non-lethal level. This was changed to a factor of 3, resulting in 10-minute through 8-hour values of 40,000 to 1400 ppm (see table below). The 10-minute 40,000 ppm value exceeds the 50% lower explosive limit and therefore will not be placed in the Executive Summary table. It was moved by Bob Benson and seconded by Ernie Falke to accept the values. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (Appendix B).

A LOA of 8.9 ppm for methanol was derived with the default procedure based on the odor threshold reported by Hellman and Small (1974). The value was accepted by a unanimous show of hands.

Summary of Interim AEGL Values for Methanol						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	670 ppm	670 ppm	530 ppm	340 ppm	270 ppm	Pharmacokinetic study (Batterman et al. 1998 and others)
AEGL–2	11,000 ppm*	4000 ppm	2100 ppm	720 ppm	510 ppm	NOAEL- developmental effects in mice (Rogers et al. 1993; 1995)
AEGL–3	**	14,000 ppm*	7100 ppm*	2200 ppm	1400 ppm	Clinical treatment value (Am. Acad. Clin. Toxicol. 2002)

*The 10-minute AEGL-2 value and the 30-minute and 1-hour AEGL-3 values are higher than 1/10 of the lower explosive limit (LEL) of methanol in air (LEL = 55,000; 1/10th LEL = 5500 ppm). Therefore, safety considerations against the hazard of explosion must be taken into consideration.
**The 10-minute AEGL-3 value of 40,000 ppm is higher than 50% of the lower explosive limit of methanol in air (LEL = 55,000 ppm; 50% of the LEL = 27,500 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

Phenol (CAS No. 108-95-2)

Staff Scientist: Peter Griem, FoBiG, GmbH
Chemical Manager: Bob Snyder, Rutgers

Peter Griem addressed the major COT/AEGL comments which were as follows: (1) the phenol values are too conservative and the ERPG values are more consistent with the toxicologic profile; (2) the use of a NOAEL from a two-week study for the AEGL-1 is too conservative; (3) the NAC needs to reconsider the basis for the AEGL-2 (a fraction of the AEGL-3 values); and (4) the validity of the AEGL-3 key study is questionable (Attachment 5).

The NAC decided to retain the AEGL-1 key study, which is a repeat-exposure study (CMA 1998; Hoffman et al. 1999), but add support from a 90-day study with monkeys [5 ppm NOAEL for lung histopathology, exposures 24 hours/day, no cumulative effect (Sandage 1961)]. The interspecies uncertainty factor of 3 was reduced to 1 and the intraspecies uncertainty factor of 3 was retained. Although irritation was the endpoint, the values were time-scaled rather than flatlined as is usually done for irritants. It was moved by Marc Ruijten and seconded by John Hinz to accept the revised values. The motion passed (YES: 13; NO: 6; ABSTAIN: 1) (Appendix C).

The basis for the AEGL-2, originally derived by dividing the AEGL-3 by 3, was changed to a combination of the two studies originally used for the AEGL-3 (Flickinger 1976; Brondeau et al. 1990). Although both studies had shortcomings, i.e., aerosol exposures, nominal concentrations, and no description of toxic signs in one study, taken together, they had consistent results. Flickinger (1976) established a LOAEL for irritative effects in the rat and Brondeau et al. (1990)

established a NOAEL. The 8-hour exposure (based on Flickinger [1976]) of rats to 900 mg/m^3 (234 ppm) was used as the point of departure. Based on the small data base and study shortcomings, a modifying factor of 2 was applied. The resulting value was adjusted by inter- and intraspecies uncertainty factors of 3 each, for a total of 10, and time-scaled to the shorter exposure durations with the default n value of 3. It was moved by George Woodall and seconded by George Alexeeff to accept the values. The motion carried (YES: 17; NO: 2; ABSTAIN: 1) (Appendix C). (Note: Apparently the AEGL-2 values were mistakenly time-scaled from a 4-hour exposure to 234 ppm, and no modifying factor was applied. The AEGL-2 values for 10 minutes through 8 hours, based on the correct point of departure, are 29, 29, 23, 15, and 12 ppm. The correct values will be voted on at a future meeting.) The explanation of reduction of the intraspecies uncertainty factor to 3 based on a metabolic component will be removed from the TSD. Information from the SIDS document will be added.

Due to a lack of reliable data, an AEGL-3 was not derived. It was moved by John Hinz and seconded by Bob Benson to accept this conclusion. The motion passed by a unanimous show of hands.

Peter discussed the Level 1 study (TNO 1988) used to derive a LOA of 0.25 ppm. It was moved by Richard Thomas and seconded by John Hinz to accept the LOA. The motion passed by a unanimous show of hands.

Summary of Interim AEGL Values for Phenol

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	19 ppm	19 ppm	15 ppm	9.5 ppm	6.3 ppm	NOAEL for irritation - rat (CMA 1998; Hoffman et al. 1999)
AEGL–2	47 ppm	47 ppm	37 ppm	23 ppm	12 ppm	Sensory irritation, CNS effects - rat (Flickinger 1976; Brondeau et al. 1990)
AEGL–3	*NR	NR	NR	NR	NR	

*NR: Numeric values for AEGL-3 are not recommended because data are not available.

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

Staff Scientist: Claudia Troxel, CMTox, Inc.
Chemical Manager: Tom Hornshaw, Illinois EPA

Tom Hornshaw discussed the limited data base and the COT/AEGL recommendation that values not be derived for BCl_3 (Attachment 6). If values are derived, the COT/AEGL recommended the following: derive AEGL-2 values by dividing the AEGL-3 by 3 and do not derive an AEGL-1 (the

present AEGL-1 and -2 values were based on 1/3 of the HCl values). The COT/AEGL agreed with the method of deriving the AEGL-3. The NAC agreed to table the values until more data are available. The motion was made by John Hinz and seconded by Warren Jederberg; the motion carried unanimously by a show of hands. The chemical will be removed from the web site, and in its place, a statement will indicate that this chemical is under review.

Chlorine Trifluoride (CAS No. 7790-91-2)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bob Benson, USEPA

The COT/AEGL recommended reorganizing the document and revising the basis for the AEGL-3 values. The AEGL-3 should be based on primate data because regarding respiratory rate, gross respiratory tract anatomy, amount and distribution of types of respiratory epithelium, and airflow pattern, primates are better models for human uptake and deposition of irritants than is the rodent. Furthermore, with the use of primate data the interspecies uncertainty factor of 3 can be reduced. Sylvia Talmage described derivation of a new value of n which resulted in a slight adjustment of the AEGL-2 values (Attachment 7). It was moved by Bob Benson and seconded by Bill Bress to accept the adjusted AEGL-2 values. The motion passed (YES: 19; NO: 0; ABSTAIN: 0) (Appendix D). Based on the primate data and interspecies and intraspecies uncertainty factors of 2 and 3, respectively, the new AEGL-3 values of 84, 36, 21, 7.3, and 7.3 were suggested. The 4- and 8-hour AEGL-3 values were set equal because the 8-hour time-scaled value of 4.3 ppm was inconsistent with the overall data base. A motion to make the change was made by Ernie Falke and seconded by Richard Thomas. The motion carried (YES: 16; NO: 2; ABSTAIN: 1) (Appendix D).

Summary of Interim AEGL Values for Chlorine Trifluoride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	Slight irritation - dog (Horn and Weir 1956)
AEGL–2	8.1 ppm	3.5 ppm	2.0 ppm	0.70 ppm	0.41 ppm	Threshold, impaired ability to escape - dog (Horn and Weir 1955)
AEGL–3	84 ppm	36 ppm	21 ppm	7.3 ppm	7.3 ppm	No deaths in primates (MacEwen and Vernot 1970)

REVIEW of PRIORITY CHEMICALS

2,4-Dinitroaniline (CAS No. 97-02-9)

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

Sylvia Talmage reported that there are no reliable inhalation data on this chemical (Attachment 8). 2,4-Dinitroaniline is a solid material with a low vapor pressure. Bob Benson moved and Ernie Falke seconded a motion to table this chemical. The NAC agreed with the motion by a unanimous show of hands.

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

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

Ernie Falke reported that Kowetha Davidson had recently received the full report (Bomhard et al. 2000) on which AEGL values for sulfur chloride would be based. This chemical will be discussed at a future meeting.

Methacrylic Acid (CAS No. 79-41-4)

Staff Scientist: Fritz Kalberlah, FoBig GmbH
Chemical Manager: Bob Benson, U.S. EPA

Peter Griem updated the NAC on COT/AEGL comments on acrylic acid which might impact the derivation of values for other acrylates. The COT/AEGL suggested changing the key study for the AEGL-3; they consider the present key study - an aerosol study - inappropriate. Time-scaling will be changed to default values. The interim report has not yet been published. For comparison purposes, all acrylate values discussed at this meeting are summarized in a table following the discussions of all acrylates.

Fritz Kalberlah then discussed available data for methacrylic acid, a direct-acting irritant (Attachment 9). The studies consisted of a workplace monitoring study and several repeat-exposure studies with rats and mice. The suggested AEGL-1 of 6.7 ppm was based on irritant effects (rhinitis, minimal to mild degeneration of olfactory epithelium) in the upper respiratory passages of rats exposed to 20 ppm for 6 hours/day for 4 exposures (interspecies and intraspecies uncertainty factors of 1 and 3, respectively). Rodents are more susceptible than humans to effects in the upper respiratory tract as shown by data on acrylic acid. Marc Ruijten suggested an alternative approach: a single exposure to 100 ppm with no effects, but no histological examinations; interspecies and intraspecies uncertainty factors of 3 each for a value of 10 ppm across time. The motion was seconded by Steve Barbee. The motion failed (YES: 7; NO: 7; ABSTAIN: 2) (Appendix E). It was then moved by Richard Thomas and seconded by Ernie Falke that the originally suggested value of 6.7 ppm be used across time. The motion passed (YES: 12; NO: 5; ABSTAIN: 0) (Appendix E). The other CIIT (1984) study will be used as support.

The AEGL-2 was based on a NOAEL for the endpoint of ulceration and degeneration of the olfactory epithelium in rats and mice following four exposures to 100 ppm for 6 hours/day (CIIT 1984). Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied. Time scaling was based on the default values of 1 for longer time intervals and 3 for shorter time intervals. It was moved by John Hinz and seconded by George Woodall that the values be accepted. The motion carried (YES: 15; NO: 0; ABSTAIN: 2) (Appendix E).

The AEGL-3 was based on the lower 5% confidence limit of the benchmark dose ($BMDL_{05}$) of 1414 ppm in a 4-hour study with rats (Dupont 1993). Inter- and intraspecies uncertainty factors of 3 each were applied as well as default time scaling. It was moved by Bob Benson and seconded by John Hinz that the values be accepted. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (Appendix E).

Summary of AEGL Values for Methacrylic Acid						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	Nasal irritation - rats and mice (CIIT 1984)
AEGL–2	76 ppm	76 ppm	61 ppm	38 ppm	25 ppm	Nasal epithelial degeneration - rats and mice (CIIT 1984)
AEGL–3	280 ppm	280 ppm	220 ppm	140 ppm	71 ppm	$BMCL_{05}$ - rat (Dupont 1993)

Methyl Methacrylate (CAS No. 80-62-6)

Staff Scientist: Fritz Kalberlah, FoBig GmbH
Chemical Manager: Bob Benson, U.S. EPA

Fritz Kalberlah discussed the human and animal data available for derivation of AEGL values for methyl methacrylate, an irritant and corrosive chemical (Attachment 10). The NAC decided to use human rather than animal data as the basis for the AEGL-1. The point of departure was a NOAEL of 50 ppm for upper respiratory tract irritation in occupational monitoring studies (Cromer and Kronveter 1976; Roehm 1994). An uncertainty factor of 3 was applied to protect sensitive individuals. The resulting 17 ppm was applied to all exposure durations. A rat study (Pinto 1977) that results in essentially the same value will be used as support. The motion to use the human data was made by Marc Ruijten and seconded by Richard Thomas. The motion carried (YES: 17; NO: 0; ABSTAIN: 1) (Appendix F).

The point of departure for the AEGL-2 was a single 6-hour exposure of rats to 200 ppm which resulted in moderately severe irritation and atrophy and degeneration of the olfactory epithelium (Mainwaring et al. 2001). Another study in rats with a single exposure to 200 ppm for 6 hours

showed degeneration and necrosis of the olfactory epithelium in 3 of 5 animals (Jones, 2002). Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied. An interspecies factor of 1 was used because rodents are more susceptible than humans to effects in the upper respiratory tract as shown by data on acrylic acid. Time scaling was based on the default values of 1 for longer time intervals and 3 for shorter time intervals. Because the study was of 6 hours duration, the 10 minutes value was set equal to the 30 minute value. It was moved by Bob Benson and seconded by George Woodall that the values be accepted. The motion carried (YES: 14; NO: 1; ABSTAIN: 3) (Appendix F).

The AEGL-3 was based on the lower 5% confidence limit of the benchmark dose ($BMDL_{05}$) of 3125 ppm in a 4-hour study with rats (Tansey et al., 1980). Inter- and intraspecies uncertainty factors of 3 each were applied as well as default time scaling. It was moved by Bob Benson and seconded by Ernie Falke that the values be accepted.. The motion carried (YES: 18; NO: 0; ABSTAIN: 0). (Appendix F).

A LOA of 0.11 ppm was derived with the default procedure. John Hinz moved to accept the proposed LOA. Warren Jederberg seconded motion. The value was accepted by a show of hands.

Summary of AEGL Values for Methyl Methacrylate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	17 ppm	17 ppm	17 ppm	17 ppm	17 ppm	Upper respiratory tract irritation - humans (Cromer and Kronveter 1976; Roehm 1994)
AEGL-2	150 ppm	150 ppm	120 ppm	76 ppm	50 ppm	Nasal epithelial degeneration - rats (Mainwaring et al. 2001; Jones, 2002)
AEGL-3	630 ppm	630 ppm	500 ppm	310 ppm	160 ppm	$BMCL_{05}$ - rat (Tansy et al., 1980)

Ethyl Acrylate (CAS No. 140-88-5)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: George Woodall, U.S. EPA

Carol Wood discussed the available human and animal data (Attachment 11). For the AEGL-1, a suggested multiple-exposure study with monkeys was replaced with a single exposure study (Frederick et al. 2002) identified by Peter Griem and Fritz Kalberlah. The point of departure was a NOAEL for clinical signs and olfactory epithelial damage in rats following 1 hour of exposure to 25 ppm. The resulting value of 8.3 ppm was used across all exposure durations. It was moved

by Marc Ruijten and seconded by John Hinz that the values be accepted. The motion carried (YES: 16; NO: 3; ABSTAIN: 0) (Appendix G). The repeat exposure study with monkeys will be used as support.

The AEGL-2 was based on a 3-hour exposure of monkeys to 75 ppm which produced lesions in 15% of the olfactory epithelium (Harkema et al. 1997). The value was adjusted with inter- and intraspecies uncertainty factors of 1 and 3, respectively. In the absence of chemical-specific data, time-scaling n values of 3 for shorter exposure durations and 1 for longer exposure durations were applied. A motion was made by Ernie Falke and seconded by Bob Benson to accept the values. The motion carried (YES: 15; NO: 1; ABSTAIN: 1) (Appendix G).

Several methods were used to calculate the threshold for lethality. Data from two studies (Nachreiner and Dodd 1989; Oberly and Tansy 1985) were combined (five data points for 4 hours and three data points for 1 hour), and a $BMDL_{05}$ was calculated by Marc Ruijten. Inter- and intraspecies uncertainty factors of 3 each were applied. The program also calculated a time-scaling n value of 1.3. It was moved by Bob Snyder and seconded by Marc Ruijten that the resulting values be accepted. The motion carried (YES: 13; NO: 0; ABSTAIN: 3) (Appendix G).

Summary of AEGL Values for Ethyl Acrylate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	No nasal lesions - rats (Frederick et al. 2002)
AEGL–2	66 ppm	45 ppm	36 ppm	19 ppm	9.4 ppm	Nasal epithelial lesions - rats (Harkema et al. 1997)
AEGL–3	950 ppm	410 ppm	240 ppm	71 ppm	41 ppm	$BMCL_{05}$ - rat (Nachreiner and Dodd 1989; Oberly and Tansy 1985)

n-Butyl Acrylate (CAS No. 141-32-2)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: George Woodall, U.S. EPA

Carol Wood discussed the available human and animal data (Attachment 12). For the AEGL-1, a single 30-minute exposure of the mouse to 30 ppm would result in no irritation (1/10th of the RD_{50}) (Kirkpatrick 2003). It was moved by George Woodall and seconded by Nancy Kim to use 10 ppm across time. The motion failed (YES: 6; NO: 5; ABSTAIN: 4) (Appendix H). It was then moved by Bill Bress and seconded by John Hinz to use a 6-hour multiple-day exposure to 25 ppm

which resulted in no irritation in the rat. This value was divided by interspecies and intraspecies uncertainty factors of 1 and 3, respectively. No time-scaling was applied; the resulting 8.3 ppm was used for all exposure durations. The motion passed (YES: 15; NO: 3; ABSTAIN: 2) (Appendix H).

Several studies, as well as dividing the AEGL-3 by 3, were considered for the AEGL-2. A subchronic study with rats inhaling 211 ppm, and conducted 6 hours/day, 5 days/week, for 13 weeks (Klimisch et al. 1978) was chosen. The value was adjusted by inter- (1) and intraspecies (3) uncertainty factors and time scaled from the 6-hour exposure duration using the default n values of 3 for shorter exposure durations and 1 for longer exposure durations. The motion to accept the values was made by Ernie Falke and seconded by Marc Ruijten. The motion carried (YES: 15; NO: 0; ABSTAIN: 0) (Appendix H).

The $BMDL_{05}$ of 1652 ppm from a 4-hour study with rats (Oberly and Tansy 1985) was used as the basis for the AEGL-3. The value was adjusted with inter- and intraspecies uncertainty factors of 3 each. Time-scaling used the n value of 1.3 from the data on ethyl acrylate. It was moved by Marc Ruijten and seconded by John Hinz that the resulting values be accepted. The motion carried (YES: 13; NO: 0; ABSTAIN: 2) (Appendix H).

Summary of AEGL Values for n-Butyl Acrylate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	NOAEL for respiratory irritation - rat (Rohm and Haas 1992)
AEGL–2	160 ppm	160 ppm	130 ppm	81 ppm	53 ppm	Nasal lesions - rat (Klimisch et al. 1978)
AEGL–3	820 ppm	820 ppm	480 ppm	170 ppm	97 ppm	$BMCL_{05}$ - rat (Oberly and Tansy 1985)

Methyl 2-Chloroacrylate (CAS No. 80-63-7)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: George Woodall, U.S. EPA

In the absence of relevant data (Attachment 13), Richard Thomas moved and George Woodall seconded a motion to table the value. Production data will be pursued.

Summary Table of AEGL Values for Acrylates

AEGL-1					
Chemical	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
Acrylic acid	1.5	1.5	1.5	1.5	1.5
Methacrylic Acid	6.7	6.7	6.7	6.7	6.7
Methyl Methacrylate	17	17	17	17	17
Ethyl Acrylate	8.3	8.3	8.3	8.3	8.3
Butyl Acrylate	8.3	8.3	8.3	8.3	8.3

AEGL-2					
Chemical	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
Acrylic acid	68	68	46	21	14
Methacrylic Acid	76	76	61	38	25
Methyl Methacrylate	150	150	120	76	50
Ethyl Acrylate	66	45	36	19	9.4
Butyl Acrylate	160	160	130	81	53

AEGL-3					
Chemical	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
Acrylic acid	480	260	180	85	58
Methacrylic Acid	280	280	220	140	71
Methyl Methacrylate	630	630	500	310	160
Ethyl Acrylate	950	410	240	71	41
Butyl Acrylate	820	820	480	170	97

Methyl Chloride (CAS No. 74-87-3)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: George Rodgers, AAPCC

Sylvia Talmage discussed the human and animal data available for derivation of AEGL values (Attachment 14). Several well-conducted clinical studies showed that concentrations of 50-200 ppm were NOAELs for irritation and neurotoxicity. Because methyl chloride has no odor or warning properties at concentrations that may be neurotoxic, an AEGL-1 was not derived. A

motion to use NR (not recommended) for the AEGL-1 was made by Ernie Falke and seconded by Richard Thomas. The motion carried (YES: 13; NO: 4; ABSTAIN: 1) (Appendix I).

The AEGL-2 was based on several rat studies; a monitoring study was used as support (MacDonald 1964). The basis for the AEGL-2 was the absence of clinical signs in rats exposed to 1500 ppm for 6 hours/day for one day (Dodd et al. 1982) or 90 days (Mitchell et al. 1979). Based on blood uptake studies with various species, an interspecies uncertainty factor of 1 was used. Based on differences in uptake and metabolism among the human population, an intraspecies uncertainty factor of 3 was sufficient. In the absence of time-scaling information, n values of 3 for shorter durations and 1 for longer durations were applied. Because of the long exposure duration, the 10-minute value was set equal to the 30-minute value. It was moved by Tom Hornshaw and seconded by John Hinz that the resulting values be accepted. The motion carried (YES: 16; NO: 2; ABSTAIN: 0) (Appendix I).

Because data that address the threshold for lethality are conflicting and insufficient, Sylvia suggested an across-the-board AEGL-3 of >2000 ppm as guidance. However, the NAC found this value more confusing than helpful. Two studies reported no deaths in rats during the first 4 days of 5- and 12-day exposures to 5000 ppm for 6 hours/day (Morgan et al. 1982; Chellman et al. 1986). The 6-hour 5000 ppm exposure was considered the point of departure for lethality. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied. Time-scaling used the default n values of 1 and 3. Because of the long exposure duration, the 10-minute value was set equal to the 30-minute value. It was moved by George Woodall and seconded by Richard Thomas that the values be accepted. The motion carried (YES: 15; NO: 0; ABSTAIN: 2) (Appendix I).

Summary of AEGL Values for Methyl Chloride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR*	NR	NR	NR	NR	
AEGL–2	1100 ppm	1100 ppm	910 ppm	570 ppm	380 ppm	NOAEL for clinical signs - rat (Dodd et al. 1982; Mitchell et al. 1979)
AEGL–3	3800 ppm	3800 ppm	3000 ppm	1900 ppm	1300 ppm	Threshold for lethality - rat (Morgan et al. 1982; Chellman et al. 1986)

* NR: AEGL-1 values are not recommended as methyl chloride has no odor or warning properties at concentrations that may be neurotoxic.

Methyl Bromide (CAS No. 74-83-9)

Staff Scientist: Sylvia Talmage, ORNL

Chemical Manager: George Rodgers, AAPCC

Sylvia Talmage discussed the human and animal data available for derivation of AEGL values for methyl bromide, a widely-used fumigant (Attachment 15). Because methyl bromide has no odor or warning properties at concentrations that may be neurotoxic, an AEGL-1 was not derived. A motion to use NR (not recommended) for the AEGL-1 was made by George Alexeeff and seconded by Bob Benson. The motion passed by a unanimous show of hands.

The point of departure for the AEGL-2 was the conclusion from several studies with rats and dogs that 200 ppm for 4 hours was the threshold (NOAEL) for neurotoxicity (Hurtt et al. 1988; Hastings 1990; Japanese Ministry of Labour 1992; Newton 1994a). Time-scaling from rat lethality data resulted in an n value of 1.2. Interspecies and intraspecies uncertainty factors of 1 and 3 were applied. These were based on relative uptake among species and individual differences in uptake and metabolism, respectively, for the related chemical, methyl chloride. The 8-hour value was set equal to the 4-hour value because the 8-hour time-scaled value of 37 ppm is inconsistent with the data base for methyl bromide. Another part of the dog study by Newton (1994a), recalled by George Alexeeff, and involving 7-hour exposures of dogs to 158 ppm was also considered. The latter study was a NOAEL for neurotoxicity on the first day of a repeat-exposure study (decreased activity was observed on the 2nd and following days of exposure). A motion was made by Ernie Falke and seconded by John Hinz to accept the first set of values. The motion passed (YES: 11; NO: 4; ABSTAIN: 0) (Appendix J). The dog study, which resulted in slightly higher values for the shorter time periods, will be used to support the AEGL-2 values.

Based on differences in methyl halide metabolism between mice and other rodents and the unique sensitivity of mice to methyl chloride, the mouse was not considered an appropriate model for derivation of methyl bromide AEGL values. The AEGL-3 values were based on the $BMCL_{05}$ of 701 ppm computed from data in a series of 4-hour exposures of rats to various concentrations (Kato et al. 1986). This value (701 ppm) was also the highest nonlethal value in the study. The 4-hour 701 ppm concentration was adjusted by inter- and intraspecies uncertainty factors of 1 and 3, respectively, and time-scaled using $C^{1.2} \times t = k$. It was moved by John Hinz and seconded by Ernie Falke that the values be accepted. The motion carried (YES: 14; NO: 1; ABSTAIN: 2) (Appendix J).

Summary of AEGL Values for Methyl Bromide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR*	NR	NR	NR	NR	
AEGL–2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm	NOAEL for clinical signs - rat and dog (Newton 1994; Hastings 1990; Japanese Ministry of Labour 1992; Hurtt et al. 1988)

AEGL–3	3300 ppm	1300 ppm	740 ppm	230 ppm	130 ppm	$BMDL_{05}$ - rat (Kato et al. 1986)

* NR: AEGL-1 values are not recommended as methyl bromide has no odor or warning properties at concentrations that may be neurotoxic.

OTHER ISSUES

Rewording of AEGL Definition

The U.S. EPA AEGL web page currently has a two-sentence description of AEGLs. John Morawetz suggested changes to the web page definition, particularly a more accurate depiction of "once-in-a lifetime"exposures (Attachment 16). The definition currently reads,

> Acute Exposure Guideline Levels, or AEGLs, describe the dangers to humans resulting from short-term exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, or other accidental exposures.

After discussion, the NAC suggested the following changes for the web site.

> *Acute Exposure Guideline Levels, or AEGLs, *are intended to* describe the *risk* ~~dangers~~ to humans resulting from *once-in-a-lifetime or rare* ~~short-term~~ exposure*s* to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both federal and local authorities, as well as private companies, deal with emergencies involving spills, ~~or other~~ accidental exposures, *or other catastrophic events.*
>
> *Acute exposures are single, non-repetitive.

FMC Response to Peracetic Acid AEGL Values

Dr. Myra Weiner presented the FMC's comments on peracetic acid (Attachment 17). These comments may be addressed following publication of the peracetic acid values in the Federal Register.

ADMINISTRATIVE MATTERS

Paul Tobin indicated that the meeting site for NAC-33 has been approved. Marc Ruijten discussed meeting and housing arrangements for the NAC-33 meeting in The Netherlands. Further details will be sent to members via e-mail. Marquea King explained travel procedures

with the new U.S. EPA travel agency contractor. The site and time of future meetings is as follows:

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

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Sylvia Talmage, 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-32 Meeting Agenda
Attachment 2. NAC/AEGL-32 Attendee List
Attachment 3. Response to Federal Register comments for bromine
Attachment 4. Response to COT/AEGL comments on methanol
Attachment 5. Response to COT/AEGL comments on phenol
Attachment 6. Response to COT/AEGL comments on boron trifluoride
Attachment 7. Response to COT/AEGL comments on chlorine trifluoride
Attachment 8. Data analysis for 2,4-dinitroaniline
Attachment 9. Data analysis for methacrylic acid
Attachment 10. Data analysis for methyl methacrylate
Attachment 11. Data analysis for ethyl acrylate
Attachment 12. Data analysis for n-butyl acrylate
Attachment 13. Data analysis for 2-chloroacrylate
Attachment 14. Data analysis for methyl chloride
Attachment 15. Data analysis for methyl bromide
Attachment 16. Revision of "once in a lifetime" statement
Attachment 17. Discussion of peracetic acid AEGLs by FMC

LIST OF APPENDICES

Appendix A. Final meeting highlights of NAC/AEGL-31
Appendix B. Ballot for methanol
Appendix C. Ballot for phenol
Appendix D. Ballot for chlorine trifluoride
Appendix E. Ballot for methacrylic acid
Appendix F. Ballot for methyl methacrylate
Appendix G. Ballot for ethyl acrylate
Appendix H. Ballot for n-butyl acrylate
Appendix I. Ballot for methyl chloride
Appendix J. Ballot for methyl bromide

Appendix D

NAC/AEGL Meeting 33: June 14-16, 2004

Dedicate this m to Roger Garrett

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
George Alexeeff					Nancy Kim				
Steven Barbee					Glenn Leach				
Lynn Beasley					John Morawetz				
Robert Benson					Richard Niemeier				
Jonathan Borak					Marinelle Payton				
William Bress					Susan Ripple				
George Cushmac					George Rodgers				
Ernest Falke					Marc Ruijten				
Alfred Feldt					George Rusch, Chair				
John Hinz					Robert Snyder				
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.

Unanimous

NR= Not Recommended due to_____

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

Approved by Chair: _____ **DFO:** Paul Stanis **Date:** 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: LEWISITE 1 CAS Reg. No.: 541-25-3

Action: Proposed ✓ Interim _____ Other _____

Chemical Manager: Warren Jederberg Staff Scientist: Cheryl Bast

* adopt L-1 values for L-MIXTURE

NAC Member	~~AEGL1~~	AEGL2	AEGL3	LOA
George Alexeeff	*A	A	A	
Steven Barbee	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	P	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	A	A	A	
Jim Holler	A	A	A	
Tom Hornshaw	A	A	A	
Warren Jederberg	A	A	A	

NAC Member	~~AEGL1~~	AEGL 2	AEGL3	LOA
Nancy Kim	* P	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	A	A	A	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	P	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	N	Y	Y	
Marc Ruijten	P	P	Y	
George Rusch, Chair	Y	Y	Y	
Robert Snyder	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Y	P	Y	
TALLY	* 13/13			
PASS/ FAIL	UNANIMOUS	13/13	16/16	

HAND VOTE → TO USE "NR" for AEGL

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(0.65)	,(0.23)	,(0.12)	,(0.035)	,(0.018)
AEGL 3	,(3.9)	,(1.4)	,([redacted])	,(0.21)	,(0.11)
LOA	0.74				
* = ≤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.

* R. NIEMEIER / S. RIPPLE - Motion to use L-1 for L-MIXTURE

NR= Not Recommended due to No data available to set AEGL-1

AEGL 1 Motion by: THOMAS Second by: WOODALL
AEGL 2 Motion by: SNYDER Second by: RODGERS
AEGL 3 Motion by: M RUIJTEN Second by: R. NIEMEIER
LOA Motion by: _____ Second by: _____

Approved by Chair: _____ DFO: Paul S. Tobin Date: 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: ADAMSITE (DM) CAS Reg. No.: 578-94-9

Action: Proposed ✓ Interim _____ Other _____

Chemical Manager: Warren Jederberg Staff Scientist: Bob Young

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A	A	A		Nancy Kim	Y	Y	Y	
Steven Barbee	Y	Y	Y		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Y		John Morawetz	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Jonathan Borak	A	A	A		Marinelle Payton	A	A	A	
William Bress	Y	Y	Y		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rodgers	Y	Y	Y	
Ernest Falke	Y	Y	Y		Marc Ruijten	Y	N	Y	
Alfred Feldt	A	A	A		George Rusch, Chair	Y	Y	Y	
John Hinz	A	A	A		Robert Snyder	Y	Y	Y	
Jim Holler	A	A	A		Richard Thomas	Y	Y	Y	
Tom Hornshaw	A	A	A		George Woodall	Y	Y	Y	
Warren Jederberg	A	A	A						
					TALLY	16/16	15/16	16/16	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.20)	,(0.042)	,(0.016)	,(0.0022)	,(0.00084)
AEGL 2	,(9.7)	,(6.8)	,(2.6)	,(0.36)	,(0.14)
AEGL 3	,(21)	,(17)	,(6.4)	,(0.91)	,(0.34)
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: Niemeier Second by: Thomas
AEGL 2 Motion by: Snyder Second by: Woodall
AEGL 3 Motion by: Barbee Second by: Bress
LOA Motion by: _____ Second by: _____

Approved by Chair: [signature] DFO: Paul S. Tobin Date: 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: METHYL DICHLORO ARSINE (MD) **CAS Reg. No.:** 593-89-5

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

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff		A	A		Nancy Kim		Y	Y	
Steven Barbee		Y	Y		Glenn Leach		Y	Y	
Lynn Beasley		Y	Y		John Morawetz		A	A	
Robert Benson		P	Y		Richard Niemeier		Y	Y	
Jonathan Borak		A	A		Marinelle Payton		A	A	
William Bress		Y	Y		Susan Ripple		Y	Y	
George Cushmac		Y	Y		George Rodgers		Y	Y	
Ernest Falke		Y	Y		Marc Ruijten		P	P	
Alfred Feldt		A	A		George Rusch, Chair		Y	Y	
John Hinz		A	A		Robert Snyder		N	Y	
Jim Holler		A	A		Richard Thomas		Y	Y	
Tom Hornshaw		A	A		George Woodall		Y	Y	
Warren Jederberg		A	A						
					TALLY	14/14	13/14	15/15	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(0.63)	,(0.14)	,(0.053)	,(0.015)	,(0.0063)
AEGL 3	,(1.9)	,(0.42)	,(0.16)	,(0.044)	,(0.019)
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 Insufficient Data

AEGL 1 Motion by: Benson **Second by:** Niemeier
AEGL 2 Motion by: Niemeier **Second by:** Barbee
AEGL 3 Motion by: Rodgers **Second by:** Benson
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: ETHYLDICHLOROARSINE (ED) **CAS Reg. No.:** 598-14-1

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

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

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

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	A	A	A	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Robert Snyder	N	N	N	
Richard Thomas	Y	Y	Y	
George Woodall	Y	Y	Y	
TALLY	14/15	14/15	14/15	
PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(0.17)	,(0.059)	,(0.029)	,(NR)	,(NR)
AEGL 3	,(0.52)	,(0.17)	,(0.086)	,(NR)	,(NR)
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 Lack of data.

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: PHENYL DICHLOROARSINE (PD) **CAS Reg. No.:** 696-28-6

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

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

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

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,(0.37)	,(0.12)	,(0.061)	,(NR)	,(NR)
AEGL 3	,(1.1)	,(0.37)	,(0.18)	,(NR)	,(NR)
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 Lack of data

AEGL 1 Motion by: Rodgers **Second by:** Niemeier
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:** 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: DIPHENYLCHLOROARSINE CAS Reg. No.: 712-48-1

Action: Proposed ✓ Interim _____ Other _____

Chemical Manager: Warren Jederberg Staff Scientist: Bob Young

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(1.1)	,(0.79)	,(0.39)	,(0.098)	,(0.049)
AEGL 3	,(3.4)	,(2.4)	,( ).2)	,(0.30)	,(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 Lack of Data

AEGL 1 Motion by: Niemeier Second by: 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: 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

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

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

Chemical Manager: **Staff Scientist:** Cheryl Bast

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A	A	A	
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	A	A	A	
Jim Holler	A	A	A	
Tom Hornshaw	A	A	A	
Warren Jederberg	A	A	A	

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

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	5.5 ,( )	5.5 ,( )	4.3 ,( )	1.1 ,( )	1.1 ,( )
AEGL 3	24 ,( )	17 ,( )	13 ,( )	3.3 ,( )	3.3 ,( )
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 Lack of Data

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

Approved by Chair: _____ **DFO:** _____ **Date:** 6/14/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: HEXANE [redacted] CAS Reg. No.: 110-54-3

Action: Proposed ✓ Interim _____ Other _____

Chemical Manager: Al Feldt Staff Scientist: Peter Boo

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

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	N	
Glenn Leach	Y	Y	N	
John Morawetz	A	A	A	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Y	Y	N	
Susan Ripple	Y	Y	Y	
George Rodgers	Y	P	Y	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	P	Y	Y	
Robert Snyder	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	P	Y	Y	
TALLY	15/15	15/15	14/17	
PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (NR)	, (NR)	, (NR)	, (NR)	, (NR)
AEGL 2	* 4600 , ( )	* 3300 , ( )	* 3300 , ( )	* 3300 , ( )	* 3300 , ( )
AEGL 3	*** SEE , (BELOW)	** SEE , (BELOW)	** SEE , (BELOW)	** SEE , (BELOW)	** SEE , (BELOW)
LOA					
* = ≥10% LEL					
** = ≥50% LEL		8,600	8,600	8,600	8,600
*** = ≥100% LEL	12,000				

*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 Lack of data.

AEGL 1 Motion by: Benson Second by: Falke
AEGL 2 Motion by: Falke Second by: Benson
AEGL 3 Motion by: Falke Second by: Ruijten
LOA Motion by: _____ Second by: _____

Approved by Chair: [signature] DFO: Paul S. Tobin Date: 6/15/04

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: METHYLENE CHLORIDE CAS Reg. No.: 75-09-2

† DRAFT
Action: ~~Proposed~~ ✓ Interim_____ Other_____

Chemical Manager: AL Feldt Staff Scientist: Peter Box

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	A	A	A	
Steven Barbee	Y	P	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	A	A	A	
Jim Holler	A	A	A	
Tom Hornshaw	A	A	A	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	A	A	A	
Richard Niemeier	P	P	P	
Marinelle Payton	Y	Y	Y	
Susan Ripple	P	P	P	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	N	P	
George Rusch, Chair	Y	Y	Y	
Robert Snyder	Y	Y	Y	
Richard Thomas	Y	N	Y	
George Woodall	Y	Y	Y	
TALLY	15/15	12/14	14/14	
PASS/ FAIL	P	P	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	290 ,( )	230 ,( )	200 ,( )	,(NR)	,( )
AEGL 2	1700 ,( )	1200 ,( )	560 ,( )	100 ,( )	60 ,( )
AEGL 3	12,000 ,( )	8500 ,( )	5900 ,( )	4900 ,( )	2100 ,( )
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.

† Based on member agreement on PROVISIONAL DRAFT values which will then be [illegible] Dec, 2004 AEGL meeting for re-vote to establish Proposed AEGL val

NR= Not Recommended due to_____

AEGL 1 Motion by: Woodall Second by: Thomas
AEGL 2 Motion by: Rodgers Second by: Woodall
AEGL 3 Motion by: Snyder Second by: Falke
LOA Motion by: _____ Second by: _____

Approved by Chair: [signature] DFO: Paul Tobin Date: 6/15/04

NAC/AEGL Meeting 33: June 14-16, 2004

Decision to use model (PBPK) if sufficient info available

Chemical: ~~[redacted]~~ **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

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

*UNANIMOUS by show of hands

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:** Snyder **Second by:** Rodgers
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/15/04

Appendix O

NAC/AEGL Meeting 33: June 14-16, 2004

Chemical: SULFURIC ACID **CAS Reg. No.:** 7664-93-9

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

Chemical Manager: NANCY KIM **Staff Scientist:** JOHAN SCHEFFERLIE

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

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

PPM (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.20)	,(0.20)	,(0.20)	,(0.20)	,(0.20)
AEGL 2	,(8.7)	,(8.7)	,(8.7)	,(8.7)	,(8.7)
AEGL 3	270 ,(~~265~~)	200 ,(~~[illegible]~~)	160 ,(~~[illegible]~~)	,(110)	,(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.

Niemeier / Benson - Values apply to oleum and SO_3

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Thomas **Second by:** Kim
AEGL 2 **Motion by:** Niemeier **Second by:** Ripple
AEGL 3 **Motion by:** Kim **Second by:** Thomas
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair:_____ **DFO:** Paul S. Tobin **Date:** 6/15/04