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

April 19-21, 2004

Final 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~~ exposures 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.

*Addendum to Minutes: Methanol

At NAC-32 (April, 2004), the AEGL Committee decided to change the derivation basis for AEGL-3 for methanol from the analysis of case reports to using the clinical practice guideline. It was determined that was the Perkins model using the Vmax and Km values could be utilized. Peter Griem had changed those in the Interim-1 version (which was criticized by NAS/COT) because calculations with the original model parameters were not compatible with measured blood methanol concentrations when calculations were performed for long periods of time (40-50 hours). The AEGL Committee left the AEGL-2 values unchanged in order to maintain the basis of the derivation and the UFs used. However, the fact that the change in the model parameters would affect the results calculated for the AEGL-2 was overlooked. Using the original Perkins parameters, the values for the longer time periods changed at the last significant figure: 4 hours from 720 to 730 ppm and at 8 hours from 510 to 520 ppm. This should explain the changes in the AEGL-2 compared to the description in the NAC-32 minutes. In the derivation of AEGL-2, a UF was applied directly to the blood methanol concentration before doing model calculations. In the derivation of AEGL-3 values, the UF was applied to the calculated methanol concentration in air after model calculations. Peter Griem felt that the NAS-COT would interpret this as a inconsistency between the AEGL-2 and AEGL-3 derivation and therefore recalculated the AEGL-3 applying UFs to blood methanol concentration to be consistent with AEGL-2. As a result, the AEGL-3 values differ slightly from what the Committee has voted on in April 04: 1 hour: 7200 instead of 7100 ppm, 4 hours: 2400 instead of 2200 ppm, 8 hours: 1600 instead of 1400 ppm. Applying the UFs to calculated methanol concentrations in air for both AEGL-2 and AEGL-3 would created a different inconsistency, because then the Perkins model would be used to calculate air concentrations leading to blood methanol concentrations of 487 mg/l (for AEGL-2) and 500 mg/l (for AEGL-3). The values refer to blood concentrations in different species (i.e., mouse and man, respectively). The difference in the resulting AEGLs is a result of using UFs of 10 for AEGL-2 and 3 for AEGL-3.

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