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

September 21-23, 2004

Final Meeting-34 Highlights

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

INTRODUCTION

Chairman George Rusch welcomed the committee, as well as industry guests who included Andrew Jaques, Bill Gulledge,and Bill Snellings from the American Chemistry Council (ACC), and John Thomas (Texas), and Cynthia Mann (ExxonMobil). The draft NAC/AEGL-33 meeting highlights were reviewed. Several editorial corrections were suggested. A motion was made by Mark Ruijten and seconded by Robert Snyder to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a voice vote (Appendix A). The final version of the NAC/AEGL-33 meeting highlights is attached (Appendix B).

George Rusch discussed the last COT meeting (August 2004, Woods Hole), at which 16 documents were reviewed and about 9 were finalized. The COT put together a list of items that need to be included as an addendum to the SOP. It was suggested that the Chemical Managers should take more careful notes during the TSD author's presentation, to help capture the essence of the discussion such as the uncertainty factor rationale.

Ernest Falke made some points regarding use of uncertainty factors (UFs). He noted that UFs >30 are generally too large, and that it would be worth knowing how often we have used a 3-fold reduction of the AEGL-3 values to obtain AEGL-2 values. EPA has some database information relevant to use of uncertainty factors. Richard Niemeier noted that NIOSH has some useful information on chemical classes.

Marquea King presented a summary of the development and use of RD_{50} values by the scientific community. The issue remains as to when and how should the NAC/AEGL use RD_{50} values in AEGL development. An electronic copy of the presentation was put on the Bulletin Board. Marquea will coordinate work by those interested (John Hinz, Peter Bos, etc.) in this topic. John Hinz briefly spoke about Jet Fuels, which used RD_{50} values as part of the UF justification. He or Sylvia Talmage will update the committee on the Jet fuels TSD in March.

The highlights of the NAC/AEGL-34 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-34 Agenda.

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 three interim chemicals were discussed. Tetranitromethane and acetone cyanohydrin were reviewed by COT/AEGL at its January 2004 meeting, and the comments were published in the Eleventh Interim Report (July 2004). Propylene oxide was reviewed by COT/AEGL at its July 2003 meeting, and the comments were published in the Tenth Interim Report (January 2004).

Acetone Cyanohydrin (CAS No. 75-86-5)

Staff Scientist: Peter Griem, Germany (absent)
Chemical Manager: Ernest Falke, U.S. EPA

Ernest Falke discussed the comments made by COT on acetone cyanohydrin at the January 2004 meeting (Attachment 3). The COT suggested that the mechanism of action needs revising, and the interspecies UF of 3 can be used because the mechanism is exactly the same for all species. The COT felt that it was inappropriate to use a repeat-exposure study to derive AEGL-1 values, and instead recommended using the hydrogen cyanide values. It was moved by George Rogers and seconded by Tom Hornshaw that all changes suggested by COT, including the new AEGL-1 values, be accepted. The motion carried unanimously (YES: 17; NO: 0; ABSTAIN: 0) (Appendix C).

Summary of AEGL Values for Acetone Cyanohydrin						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm	Used hydrogen cyanide values by structural analogy.
AEGL–2	Not addressed (no change).					
AEGL–3	Not addressed (no change).					

Tetranitromethane (CAS No. 509-14-8)

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

Sylvia Milanez briefed the NAC on the response of the COT (January 2004 meeting) to the tetranitromethane (TNM) TSD and reviewed the TNM data (Attachment 4). The COT recommended basing AEGL-2 and AEGL-3 values on a single-exposure study (Kinkead et al. 1977) rather than a multiple-exposure study (NTP 1990). COT also recommended eliminating the AEGL-1 due to lack of data, as the original values were recently found to have been based on an erroneous interpretation of the NTP (1990) report, after obtaining raw study data.

The new AEGL-2 and AEGL-3 values were based on the 4-hour rat LC_{50} study of Kinkead et al. (1977), in which mortality occurred at $15 ppm but not at 10 ppm [0/10]. The rats were lethargic, had a slowed rate and depth of respiration, nose and eye irritation, mild lung congestion, and premature decedents had lung congestion and hemorrhage. The AEGL-2 point of departure (POD) was 3.3 ppm, which was obtained by applying a MF of 3 to 10 ppm (lowest concentration tested) to obtain a concentration that would cause only mild reversible lung irritation. Scaling across time was performed using the default n=3 or n=1, except that the 30-minute values were adopted for 10 minutes. A total uncertainty factor of 10 was used: 3 for interspecies extrapolation because the key study tested the most sensitive species, and 3 to account for sensitive humans because mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans. The resulting AEGL-2 values were lower than those derived using a TNM inhalation cancer slope factor based on the NTP (1990) 2-year inhalation study, at a 10^{-4} theoretical excess cancer risk level. However, the NAC asked that the cancer assessment be redone using lung surface area comparison instead of body weight comparison between rats and humans for the dosimetric adjustment.

The new AEGL-3 values were based on the calculated $BMDL_{05}$ for lethality of 11 ppm (log/probit model from EPA's Benchmark Dose Software, Version 1.3.2.) using the Kinkead et al. (1977) lethality data. Scaling across time was performed as for the AEGL-2. A total uncertainty factor of 10 was applied: 3 for interspecies extrapolation (key study tested the most sensitive species), and 3 for human variability (threshold for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans).

A single motion was made by George Rodgers and seconded by Susan Ripple to accept all three sets of new AEGL values. The motion carried unanimously (YES: 20; NO: 0; ABSTAIN: 0) (Appendix D). An LOA was not developed due to lack of data.

Summary of AEGL Values for Tetranitromethane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	Not recommended due to insufficient data.					
AEGL–2	0.66 ppm	0.66 ppm	0.52 ppm	0.33 ppm	0.17 ppm	Mild reversible lung irritation in rats (Kinkead et al. 1977).
AEGL–3	2.2 ppm	2.2 ppm	1.7 ppm	1.1 ppm	0.55 ppm	$BMDL_{05}$ for lethality in rats (Kinkead et al. 1977).

Propylene Oxide (CAS No. 75-56-9)

Staff Scientist: Claudia Troxel, ORNL
Chemical Manager: Jim Holler, ATSDR

Claudia Troxel reviewed the propylene oxide July 2003 COT comments, which recommended all different values than originally proposed (Attachment 5). The NAC discussion began with the AEGL-3, and considered the relevancy of the mouse, rat, dog, monkey, and rat data. The mouse was considered overly sensitive, as it depletes glutathione more readily than other species. The rat NTP (1985) lethality data were used as the basis for developing AEGL-3 values. The calculated 4-hour, $BMCL_{05}$ of 1161 ppm was used as the point of departure. A total uncertainty factor of 3 was applied. An intraspecies UF of 3 was applied on the basis that the mechanism of toxicity, irritation, is not expected to differ greatly between individuals. The interspecies UF of 1 was applied on the basis of supporting data in dogs (similar $BMCL_{05}$; Jacobson et al., 1956), primates (300 ppm, 6 hours/day for 2 years or 457 ppm, 7 hrs/day for 154 days were not lethal; Spintz et al. 1982; Setzer et al., 1997; Lynch et al., 1983; Rowe et al., 1952), and humans (1520 ppm for 171 minutes not lethal). A value of n=1.7 was derived from the Rowe et al. (1956) study and used to scale across time, except that the 30-minute value was adopted for 10 minutes. The motion to adopt these values was made by Bob Benson and seconded by Jim Holler and passed unanimously (YES: 18; NO: 0; ABSTAIN: 0).

The AEGL-2 derivation began with a discussion about the relevance of dyspnea as an AEGL-2 endpoint, NAC concluding that dyspnea was a broad-spectrum symptom and someone with severe dyspnea would have an impaired ability to escape. The AEGL-2 was based on dyspnea in mice that inhaled 387 ppm for 4 hours (NTP, 1985). A total UF of 3 was applied. An intraspecies UF of 3 was applied because the mechanism of toxicity, irritation, is not expected to differ greatly between individuals. An interspecies UF of 1 was applied because mice were the most sensitive laboratory species tested, available data indicate that mice are equally or slightly more sensitive than humans, and dyspnea was the most sensitive endpoint (NTP reported effect at a lower concentration than any other study). Scaling across time was done as for the AEGL-3. The resulting values were supported by dog and monkey data. George Rodgers proposed and

Richard Thomas seconded that the resulting values be adopted and the motion passed (YES: 12; NO: 1; ABSTAIN: 4).

The AEGL-1 is based on the workplace survey which measured exposure concentrations of 380 ppm for 177 minutes, 525 ppm for 121 minutes; 392 ppm for 135 minutes; and 460 ppm for 116 minutes in the breathing zone of three workers during drumming operations (CMA, 1998a). Strong odor and irritation was noted in monitoring study (exact nature of the irritation, other than the strong odor, was not provided, but occasional eye irritation was noted in the report as reason for monitoring program). Because irritant effects are not scale across time, the values would be set equal across time. Therefore, the 4 exposure concentrations can be averaged together, resulting in a point of departure of 440 ppm. A total uncertainty factor and modifying factor of 6 is applied. An intraspecies uncertainty factor of 3 was applied because irritation is a point of contact effect and is not expected to vary greatly among individuals. A modifying factor of 2 is applied because the defined effects are above an AEGL-1 (undefined irritation) but below an AEGL-2 endpoint. Marc Ruijten proposed and Jim Holler seconded that the resulting values and the motion passed (YES: 13; NO: 0; ABSTAIN: 3) (Appendix E).

An LOA of 21 ppm was accepted unanimously by a hand vote.

Summary of AEGL Values for Propylene Oxide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	73 ppm	73 ppm	73 ppm	73 ppm	73 ppm	CMA, 1998a
AEGL–2	440 ppm	440 ppm	290 ppm	130 ppm	86 ppm	NTP, 1985
AEGL–3	1300 ppm	1300 ppm	870 ppm	390 ppm	260 ppm	NTP, 1985

REVIEW of PRIORITY CHEMICALS

Acetaldehyde (CAS No. 75-07-0)

Staff Scientist: Johan Schefferlie, RIVM, the Netherlands
Chemical Manager: Marinelle Payton, Jackson State University (absent)

Johan Schefferlie presented the available human and animal data for acetaldehyde, which is found in foods and formed in the metabolism of ethanol (Attachment 6). The initially proposed AEGL-1 was based on eye irritation in human volunteers exposed to 50 ppm for 15 minutes, the NOEL was 25 ppm (Silverman et al. 1946). After application of a UF of 3, this yielded 8 ppm, which was applied to all exposure durations. The developed values were considered too low and based only on nominal concentrations, so Robert Benson moved (second by John Hinz) that the AEGL-1 instead be based on the Sim and Pattle (1957) study, in which human subjects exposed to a measured concentration of 134 ppm for 30 minutes reported mild upper respiratory irritation but

no eye irritation. An intraspecies UF of 3 was applied for sensitive individuals, and the resulting value of 45 ppm was applied to all exposure durations. The motion passed (YES: 17; NO: 4; ABSTAIN: 1).

Two options were presented for developing AEGL-2 values, one being based on the NOEL for nasal pathology in the rat (1500 ppm for 6 hrs; Cassee et al. 1996b) and the second a NOEL for dyspnea (2217 ppm for 30 minutes; Appelman et al. 1982). A motion was made by Marc Ruijten and seconded by Bob Benson to use option 1 and default time extrapolation (n=3 or n=1) and apply an interspecies UF of 1 (effect was below the threshold for AEGL-2) and an intraspecies UF of 3, yielding 1100, 1100, 800, 500, and 380 ppm for 10, 30, 60, 240, and 480 minutes, respectively. This motion failed (YES: 2; NO: 20; ABSTAIN: 0). Another motion was made (George Woodall; second by Richard Thomas) also based on option 1 but using an interspecies UF of 1 and an intraspecies UF of 10 (considerable variation among humans), yielding 340, 340, 270, 170, and 110 ppm, respectively. This motion passed (YES: 20; NO: 2; ABSTAIN: 0).

AEGL-3 values were based on a rat lethality study (Appelman et al. 1982) from which a BMDL05 of 5295 ppm was calculated for a 4-hour exposure. To this level a total uncertainty factor of 10 was applied, consisting of a factor of 3 for interspecies extrapolation and a factor of 3 for sensitive human subpopulations. Using default n= 3 or n=1, this yielded AEGL-3 values of 1100, 1100, 840, 530, and 260 ppm for 10, 30, 60, 240, and 480 minutes, respectively. The motion was made by George Alexeeff and seconded by John Hinz, and passed (YES: 20; NO: 0; ABSTAIN: 2) (Appendix F).

An LOA of 0.56 ppm was accepted unanimously by a hand vote.

Summary of AEGL Values for Acetaldehyde						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	45 ppm	45 ppm	45 ppm	45 ppm	45 ppm	Mild upper respiratory irritation in humans (Sim and Pattle 1957)
AEGL–2	340 ppm	340 ppm	270 ppm	170 ppm	110 ppm	NOEL for nasal pathology in the rat (Cassee et al. 1996b)
AEGL–3	1100 ppm	1100 ppm	840 ppm	530 ppm	260 ppm	$BMDL_{05}$ in acute rat lethality study (Appelman et al. 1982)

Vinyl Acetate (CAS No. 108-05-4)

Staff Scientist: Claudia Troxel, ORNL
Chemical Manager: Richard Thomas, INTERCET, Ltd.

Claudia Troxel presented the AEGL derivations for vinyl acetate (Attachment 7). The AEGL-1 was based on a human study (Smyth and Carpenter 1973) in which inhalation by humans of 4-20

ppm for 2 minutes caused very slight irritation whereas inhalation of 34 ppm for 2 hours caused persistent throat irritation. The POD was 20 ppm, which represents a no-effect level for notable discomfort. A total uncertainty factor of 3 was applied for intraspecies uncertainty because the slight irritation is a local effect not expected to vary greatly among individuals. The resulting value of 6.7 ppm was applied to all exposure durations. The motion was made by Marc Ruijten and seconded by George Alexeeff and passed (YES: 20; NO: 0; ABSTAIN: 2).

The AEGL-2 was based on a rat study (Bogdanffy et al. 1987) in which exposure for 6 hours to 1000 ppm caused reversible nasal lesions (cell proliferation). A visitor from DuPont (Rudy Valentine) indicated that the study pathologist (Randall Frame) considered the lesions reversible. The NAC asked that the pathologist be contacted to confirm this; if he does not, the AEGL-2 will be revisited. Default values of n=3 or n=1 were applied as well as a total UF of 10: 3 for interspecies and 3 for intraspecies variability because a higher UF would reduce the AEGL-2 values to those that did not cause serious health effects in humans. Marc Ruijten, with a second by John Hinz, made the motion to accept the resulting AEGL values and the motion carried (YES: 13; NO: 3; ABSTAIN: 6).

After some discussion of the mouse being overly sensitive, the Bogdanffy et al. (1987) 6-hour rat study was also used to derive AEGL-3 values. The POD was 1000 ppm, which caused olfactory lesions and was far below a lethal concentration. Default values of n=3 or n=1 were applied. The total UF was 3: 1 for interspecies uncertainty because the POD was far below a lethal concentration, and 3 for human variability. Bob Benson proposed and Marc Ruijten seconded that the resulting values and the motion passed (YES: 15; NO: 0; ABSTAIN: 5) (Appendix G). The NAC commented that the TSD needs to clearly state why a carcinogenicity risk assessment was not put in the Appendix.

An LOA of 0.25 ppm was accepted unanimously by a hand vote.

Summary of AEGL Values for Vinyl Acetate

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	NOEL for notable discomfort in humans (Smyth and Carpenter 1973).
AEGL–2	230 ppm	230 ppm	180 ppm	110 ppm	75 ppm	Reversible nasal lesions in rats (Bogdanffy et al. 1987).
AEGL–3	760 ppm	760 ppm	610 ppm	380 ppm	250 ppm	Reversible nasal lesions in rats as conservative estimate of lethality threshold (Bogdanffy et al. 1987).

Disulfur Dichloride (CAS No. 10025-67-9)

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

Kowetha Davidson discussed the limited data available to derive disulfur dichloride AEGL values (Attachment 8). All three sets of AEGL values were based on a recent 4-hour exposure rat study conducted by Bomhard et al. (2000). AEGL-1 values were based on the NOEL of 33.3 ppm for upper respiratory tract irritation, breathing difficulty, and other signs of discomfort seen in the rats. Because very little is known about the toxicity of inhaled sulfur chloride, and no data were available to compare the toxicity of sulfur chloride in different species or among humans, UFs of 10 for interspecies sensitivity and 10 for intraspecies variability were applied to 33.3 ppm (total = 100). Defaults values $n = 3$ and $n = 1$ were used to extrapolate to shorter and longer time frames, except that the 30-minute value was adopted for 10 minutes. The NAC did not use the 4-hour value of 0.33 ppm for all time points because disulfur dichloride is not water-soluble and there was concern about doubling the concentration in the deep lung for the 8-hour exposure duration. The motion to use the scaled AEGL values was made by Steve Barbee and seconded by George Alexeeff and passed (YES: 17; NO: 0; ABSTAIN: 2).

For AEGL-2, the POD was 242 ppm (which was within 20% of the $BMDL_{05}$), which caused upper respiratory irritation (bloody and serous nasal discharge), breathing difficulty, and reduced activity, and could impede the ability to escape. A modifying factor (MF) of 2 was applied to because the observed effects exceeded the severity of AEGL-2 and the database was deficient. A total UF of 30 was used: 10 for interspecies variability because only one animal study was available without corroborating human data, and 3 for intraspecies variability because sulfur chloride is an irritant and the response in humans is not expected to vary by more than a factor of 3. Greater MF or UFs were not used as they would cause the AEGL-2 values to approach the no-effect level. Time scaling was performed as for AEGL-1. It was moved by Steve Barbee and seconded by Ernest Falke that the values be accepted. The motion carried (YES: 16; NO: 1; ABSTAIN: 3).

The POD for the AEGL-3 was the $BMDL_{05}$ for lethality of 328 ppm, which was derived using the log/probit model from EPA's Benchmark Dose Software, Version 1.3.2. A total UF of 30 was applied: 10 for interspecies sensitivity and 3 for intraspecies variability, using the same rationale as for AEGL-2. Time scaling was performed as for AEGL-1 and AEGL-2. It was moved by Marc Ruijten and seconded by Bob Benson that the values be accepted. The motion carried (YES: 19; NO: 0; ABSTAIN: 1) (Appendix H).

An LOA was not developed due to lack of data; this statement needs to be added to the TSD.

Summary of AEGL Values for Disulfur Dichloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.67 ppm	0.67 ppm	0.53 ppm	0.33 ppm	0.17 ppm	NOEL for upper respiratory tract irritation and other signs in rats (Bomhard et al., 2000)
AEGL–2	8.1 ppm	8.1 ppm	6.4 ppm	4.0 ppm	2.0 ppm	Respiratory irritation in rats and inability to escape (Bomhard et al., 2000)
AEGL–3	19 ppm	19 ppm	15 ppm	9.6 ppm	4.8 ppm	$BMDL_{05}$ for lethality in rats (Bomhard et al., 2000)

Dibromoethane (CAS No. 106-93-4)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Nancy Kim, NY State Dept. of Health

Kowetha Davidson reviewed the human and animal data on dibromoethane, which affects the respiratory system, heart, and CNS, and is genotoxic (Attachment 9). She also noted that the ppm to mg/m^3 conversion on the handout was done backwards. There were no data from which to calculate AEGL-1 values, which were not developed.

AEGL-3 values were developed first. In the TSD, AEGL-3 values were based on the NOEL for lethality (100 ppm for 8.5 hours) in a study where rats were exposed to 100 to 10,000 ppm dibromoethane for 1.2 minutes to 16 hours (Rowe et al. 1952). The total UF of 10 included 1 for interspecies variability because PBPK modeling showed that human uptake and metabolism is at least 3-fold slower than of rats, and 10 for human variability due to polymorphisms in several metabolic enzymes. Time scaling used a data-derived n=1.4 (from this study), which yielded values of 166, 76, 46, 17, and 10 ppm. The NAC, however, derived AEGL-3 values using the same study but an alternate form of the ten Berge equation, including an interaction factor, as presented by Mark Ruijten, which yielded n=1.2 and AEGL-3 values of 96, 40, 26, 18, 13, for 10 minutes to 8 hours, respectively. The motion to accept the values, made by Richard Thomas and seconded by George Woodall, carried (YES: 15; NO: 1; ABSTAIN: 2) (Appendix I).

The NAC deferred development of AEGL-2 values to a future NAC/AEGL meeting due to lack of adequate data. In the TSD, AEGL-2 values were based on an abstract describing a developmental neurotoxicity study in which rat embryos were exposed to 65 ppm 1,2-dibromoethane, 6 hours/day for 3 days during gestation (Vodickova et al. 2003). AEGL-2 values were developed using a single exposure to 6 hours, because developmental effects can occur from a single day exposure of the fetus, and the half-life of 1,2-dibromoethane excretion after a 7-hour exposure is <6 hours. The total UF was 10 (rationale as for AEGL-3). Time scaling using n = 1.4

(see AEGL-3) yielded AEGL-2 values of 84, 38, 23, 8.7, and 5.3 ppm, respectively, for 10 minutes to 8 hours. These values could no longer be used because they intersected with the newly developed AEGL-3 values. Additionally, the NAC had doubts about the credibility of the abstract, and the use of a single exposure from a multiple-exposure developmental study to derive values.

An LOA was not developed due to lack of data, which needs to be stated in the TSD.

Summary of AEGL Values for Dibromoethane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	Not recommended due to insufficient data.					
AEGL–2	Deferred to the December, 2004 NAC/AEGL meeting due to inadequate data.					
AEGL–3	96 ppm	40 ppm	26 ppm	18 ppm	13 ppm	Rowe...

Hydroxylamine (CAS No. 7803-49-8)

Staff Scientist: Sylvia Milanez, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Sylvia Milanez presented the limited available information on hydroxylamine, which is very explosive and difficult to handle as a free base (Attachment 10). Adequate data were not available to derive AEGL-1, AEGL-2, or AEGL-3 values either for hydroxylamine, or its more stable sulfate or hydrochloride salts. A suggestion was made by the NAC that a statement should be developed for chemicals such as hydroxylamine, which are not likely to pose an inhalation hazard due to their low volatility and low potential for human exposure. Some NAC members questioned why this chemical was addressed, i.e. which agency nominated it and why.

A single motion was made by George Rodgers and seconded by Richard Thomas to not develop any AEGL values due to lack of data. The motion carried unanimously by a show of hands (Appendix J).

An LOA was not developed due to lack of data.

Summary of AEGL Values for Tetranitromethane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	Not recommended due to insufficient data.					
AEGL–2	Not recommended due to insufficient data.					
AEGL–3	Not recommended due to insufficient data.					

Cumene (CAS No. 98-82-8)

Staff Scientist: Sylvia Milanez, ORNL
Chemical Manager: John Hinz, AFIOH/RSRE

Sylvia Milanez provided a review of the background and inhalation toxicity of cumene (Attachment 11). The AEGL-1 in the TSD was based on an NTP (2004) study in which exposure to 250 ppm for 6 hours (repeatedly) was a NOEL for neurotoxic effects. The NAC initially considered not adopting AEGL-1 values (Bob Benson motioned; Nancy Kim second), but the motion failed (YES: 6; NO: 11; ABSTAIN: 1). The NAC ultimately based the AEGL-1 on an anecdotal report that exposure to 300-400 ppm was painful to the eyes and upper respiratory passages of chemical workers (Dow 1948). A modifying factor of 2 was applied to keep toxicity within the scope of AEGL-1 (mild eye and respiratory irritation), and a UF of 3 for intraspecies variability, because mild eye and respiratory irritation is not expected to vary greatly among humans. The resulting AEGL value of 50 ppm was adopted for 10 minutes to 8 hours, and was supported by a study in which volunteers willingly tolerated exposure to 49-146 ppm cumene for an 8-hour period with two 30-minute breaks (Senczuk and Litewka 1976). The motion to accept the values, made by Bob Benson and seconded by George Rodgers, carried (YES: 17; NO: 0; ABSTAIN: 1).

The POD for the AEGL-2 was exposure to 500 ppm for 6 hours, which caused mild reversible neurological changes in a rat functional observational battery (FOB) (Bushy Run 1989), and was a NOEL for ataxia and an impaired ability to escape. A total UF of 3 was applied, consisting of an interspecies UF of 1 [most sensitive species tested; greater UF would yield AEGL-2 values below those which had no effect on monkeys, rats, dogs, or guinea pigs upon repeated exposure (244 ppm 8 hours/day for 30 days; Jenkins 1970)], and an intraspecies UF of 3 (CNS depression not expected to vary more than 3-fold among humans). Scaling across time, including to 10 minutes (studies showed dose-response from 20 minutes to 6 hours), was performed using default values of n=3 or n=1. Marc Ruijten motioned, and John Hinz seconded, to accept the resulting values, and the motion passed (YES: 15; NO: 1; ABSTAIN: 1).

AEGL-3 values were based on the same study as the AEGL-2, and exposure to 1200 ppm for 6 hours was considered the lethality threshold because (1) 2000 ppm for 6 hours/day caused 100% mortality in rats and mice in 2 days (NTP 2004), and (2) up to 90 days of exposure to 1200 ppm for 6 hours/day was not lethal in several rat studies. An interspecies UF of 1 was used because the animal data showed that 1200 ppm for 6 hours was not lethal, and use of a UF of 3 would yield AEGL-3 values below AEGL-2 values. An intraspecies UF of 3 was used because CNS depression is not expected to vary by more than a factor of 3 among humans. Scaling was done as for the AEGL-2. It was noted that the 10-minute and 30-minute AEGL-3 values exceed 10% of the LEL (lower explosive limit) of cumene of 9000 ppm. Marc Ruijten motioned, and Bob Benson seconded, to accept these values, and the motion carried (YES: 17; NO: 0; ABSTAIN: 1) (Appendix K).

An LOA of 0.017 ppm was accepted unanimously by a hand vote.

Summary of AEGL Values for Cumene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	50 ppm	50 ppm	50 ppm	50 ppm	50 ppm	Mild eye and respiratory irritation in humans (Dow 1948)
AEGL–2	550 ppm	380 ppm	300 ppm	190 ppm	130 ppm	Mild reversible neurological changes and NOEL for ataxia in rats, and impaired ability to escape (Bushy Run 1989)
AEGL–3	1300 ppm*	920 ppm*	730 ppm	460 ppm	300 ppm	Lethality threshold in rats (Bushy Run 1989)

*These values exceed 10% of the LEL (lower explosive limit) of 9000 ppm.

Diketene (CAS No. 674-82-8)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: George Alexeeff, California EPA

Kowetha Davidson briefly brought up diketene, although time ran out to do a formal presentation, and the chemical will be presented at a future date.

OTHER ISSUES

Comments by Industry on Ethylene Oxide

Bill Snellings (instead of Bill Gulledge) from the ACC gave a short presentation in which he proposed alternate AEGL values for ethylene oxide (Attachment 12).

Rewording of AEGL Definition

The NAC changed one word and one phrase of the most recent definition of AEGLs to be put on the U.S. EPA AEGL web site (Attachment 13). As shown below, the word "federal" was changed to "**national**", and the phrase "non-repetitive" (in the definition of the word "acute") was changed to **"for not more than 8 hours**." Ernest Falke made the motion, and George Rodgers seconded, that the new definition be accepted. The motion carried (YES: 12; NO: 2; ABSTAIN: 0) (Appendix L). The definition now reads,

> Acute* Exposure Guideline Levels are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help

both ~~federal~~ **national** and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures.

*Definition = Acute exposures are single, ~~non-repetitive~~ **for not more than 8 hours**.

ADMINISTRATIVE MATTERS

The date and place of the next NAC/AEGL meeting (#35) was announced to be December 13-15, in Washington DC (U.S. Department of Labor). The next meeting of the NAC/COT will be February 21-23 at the Beckman Center in California.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Sylvia Milanez, Oak Ridge National Laboratory, with input from the respective staff scientists, chemical managers, and others.

LIST OF ATTACHMENTS

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

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Attachment 4. Response to COT/AEGL comments on tetranitromethane
Attachment 5. Response to COT/AEGL comments on propylene oxide
Attachment 6. Data analysis for acetaldehyde
Attachment 7. Data analysis for vinyl acetate
Attachment 8. Data analysis for disulfur dichloride
Attachment 9. Data analysis for dibromoethane
Attachment 10. Data analysis for hydroxylamine
Attachment 11. Data analysis for cumene
Attachment 12. Bill Snellings (ACC) ethylene oxide presentation
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Attachment 1
NAC - 34

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-34
September 21-23, 2004

U.S. Department of Labor
Room C5515 1A & 1B
200 Constitution Ave., N.W.
Washington, DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Tuesday, September 21, 2004

10:00 a..m.	Introductory remarks, approval of NAC/AEGL-33 Highlights, and status of FR notice (George Rusch, Ernie Falke, and Paul Tobin)
10:30	RD_{50} issue/Jet Fuel-8 (John Hinz/Marquea King)
11:15	COT meeting update (George Rusch, Ernie Falke, and Paul Tobin)
12:30 p.m.	Lunch
1:30	Review of Acetaldehyde (Marinelle Payton/Johan Schefferlie)
3:30	Break
3:45	Review of Vinyl Acetate (Richard Thomas/Claudia Troxel)
5:30	Adjourn for the day

Wednesday, September 22, 2004

8:30 a.m.	Review of Dibromoethane (Nancy Kim/Kowetha Davidson)
10:30	Break
10:45	Revisit of Acetone Cyanohydrin- COT comments (Ernie Falke/Peter Griem)
11:30	Review of Hydroxylamine (George Cushmac/Sylvia Milanez)
12:30p.m.	Lunch
1:30	Revisit of Disulfur dichloride- New data (Ernie Falke/Kowetha Davidson)
2:00	Revisit of Propylene Oxide- COT comments (Jim Holler/Claudia Troxel)
3:30	Break
3:45	Revisit of Tetranitromethane- COT comments (Ernie Falke/Sylvia Milanez)
5:30	Adjourn for the day

Thursday, September 23, 2004

8:00 a.m.	Review of Cumene (John Hinz/Sylvia Milanez)
9:30	ACC Ethylene Oxide Presentation (Bill Gulledge)
10:00	Break
10:15	Review of Diketene (George Alexeeff/Kowetha Davidson)
11:30	Administrative matters
12:00 noon	Adjourn meeting

ATTACHMENT 2

NAC/AEGL Meeting 34: September 21-23, 2004

Day 1

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

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff				
Steven Barbee		Absent PM		
Lynn Beasley				
Robert Benson				
Jonathan Borak				
William Bress				
George Cushmac				
Ernest Falke		Absent PM		
~~Alfred Feldt~~				
John Hinz				
Jim Holler				
Tom Hornshaw				
~~Warren Jederberg~~	Absent			
Iris Camacho				
MARQUEA P. KING				

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim				
Glenn Leach				
John Morawetz				
Richard Niemeier				
~~Marinelle Payton~~	Absent			
Susan Ripple				
George Rodgers				
Marc Ruijten				
George Rusch, Chair				
Robert Snyder		Present PM		
Richard Thomas				
George Woodall				
Steve Wellner (MPA)				
TALLY				
PASS/ FAIL				

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

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

NR= Not Recommended due to_____

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

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

Attachment 2

NAC/AEGL Meeting 34: September 21-23, 2004

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

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

Day 2

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	GA				Nancy Kim	NK			
Steven Barbee	SB				Glenn Leach	GL			
Lynn Beasley	LB				John Morawetz				
Robert Benson	RB				Richard Niemeier	RN			
Jonathan Borak x					~~Marinelle Payton~~	—			
William Bress	WB				Susan Ripple	SR			
George Cushmac	GEC				George Rodgers	GR			
Ernest Falke	EF				Marc Ruijten	MR			
~~Alfred Feldt~~	—				George Rusch, Chair	GR			
John Hinz	JH				Robert Snyder	RS			
Jim Holler x					Richard Thomas x				
Tom Hornshaw	TH				George Woodall	GW			
~~Warren Jederberg~~	—								
					TALLY				
					PASS/ FAIL				

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

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

NR= Not Recommended due to_____

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

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

Sept 22, 2004 Ernie

Attachment 3

ACETONE CYANOHYDRIN

Discussion of NAS-COT Comments

NAC/AEGL Meeting 34, September 19-21, 2004

The AEGL document on acetone cyanohydrin was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 28-30, 2004.

The subcommittee concluded that a revised draft can be finalized if the recommended revisions are made appropriately.

Besides several editorial comments, major concerns were

(1) that the AEGL-1 values, like the AEGL-2 and -3, should be based on the AEGL values for HCN

Editorial comments, which will be addressed in the final TSD, included:

- COT felt that the mechanism of action of cyanide was misrepresented and needed revision;

- COT questioned that an UF of 3 for toxicodynamic differences for the AEGL-1 could be justified given that the mechanism of cyanide intoxication is precisely the same in all aerobic species. [Since AEGL-1 values will be based on HCN AEGL-1 values, this comment does not need to be addressed.

- The TSD should make some notion by the AEGL values that the total of both acetone cyanohydrin and HCN concentrations should be measured and considered. Consequently, detectors need to measure the total of both acetone cyanohydrin and HCN.

Comments on AEGL-1

COT: The AEGL-1 is based on a study exposing rats for 5 days/week. There is little basis for the AEGL-1 in that study. Red nasal discharge was not consistently seen in any of the [four] Monsanto studies and, when present, was not always dose-responsive.

In addition, presence of that endpoint in control animals varied widely.

In light of the variability, red nasal discharge seems a poor endpoint on which to base AEGL-1.

Furthermore, the repeat exposure studies are not appropriate for AEGL-1 derivation.

In light of the limitations of the toxicological data, it is recommended that AEGL-1 values be derived from HCN values, as was done for AEGL-2 and -3.

Reply: AEGL-1 values should be set as suggested by NAS.

AEGL-1 Values for Acetone Cyanohydrin * (Interim 1/2003)				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
2.1 ppm	2.1 ppm	1.7 ppm	1.1 ppm	0.69 ppm

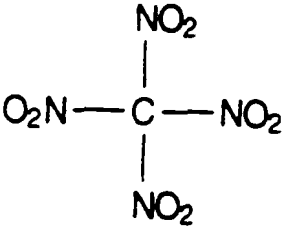
Final AEGL-1 Values for Acetone Cyanohydrin *				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
2.5 ppm	2.5 ppm	2.0 ppm	1.3 ppm	1.0 ppm

* It should be noted that acetone cyanohydrin decomposes spontaneously to yield hydrogen cyanide and acetone and that, therefore, always a mixed exposure will result from acetone cyanohydrin release. The derived values (expressed as ppm) refer to the sum of acetone cyanohydrin and hydrogen cyanide. Cutaneous absorption may occur; direct skin contact with the liquid should be avoided.

Attachment 4

NAC/Draft 3: Sept 2004

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR TETRANITROMETHANE (TNM)



Draft 3: September 2004
COT presentation: January 2004
Draft 2 to NAC: October, 2000
Draft 1to NAC: March, 1999

ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: 10/00: Ernest Falke (3/99: Kyle Blackman)
Chemical Reviewers: George Rodgers, Richard Thomas

INTRODUCTION

- TNM is explosive liquid used as oxidizer in rocket propellants, to increase cetane of diesel fuels. It is formed as an impurity (fumes) during TNT (trinitrotoluene) production.

- Effects in animals: respiratory and eye irritation, lung vascular congestion, pulmonary edema, bronchopneumonia, and lung tumors in rats and mice. Methemoglobinemia from oral but not inhalation exposure (Kinkead et al. 1977).

- No quantitative human data. No human odor threshold. **Impure** TNM (from TNT production) caused irritation of the eyes, nose, throat, dizziness, chest pain, dyspnea, pulmonary edema, pneumonia, methemoglobinemia, cyanosis, and death.

COT Major Comments on Tetranitromethane

- Throughout the document, use of the term "threshold" is not justified for lethality, NOEL is more appropriate.

Response: Replaced "threshold" with NOEL throughout document

- The AEGL-2 was derived from a 5-ppm concentration in a multiple dose mouse study (6 hr/d, 5 d/wk, 2 wks). This is appropriate when no adequate single dose study is available. However, there is a single dose study (Kinkead et al. 1977) in which rats exposed to TNM at 10 ppm for 4 hours lost weight the first 4 days and then recovered and had mild lung congestion.....

Response: Used Kinkead et al. (1977) study to derive AEGL-2 values, POD was 10 ppm divided by 3 to keep effects within scope of AEGL-2

- The multiple exposure study (NTP 1990) was used as the basis for AEGL-3 (10 ppm was considered the highest concentration below lethality, but 1/5 male rats died after 8 exposures). The single exposure study of Kinkead et al..... is a more appropriate basis. Rats are clearly more sensitive than mice, and experimentally, there are no deaths in rats at 10 ppm for 4 hours.

Response: Used Kinkead et al. (1977) to derive AEGL-3 values, POD was 10 ppm as the lethality NOEL

Derivation of AEGL– 1

- **AEGL-1 values were not developed due to insufficient data.** No studies were located with endpoints clearly within the scope of AEGL-1.

- The previous (Draft 1 and Draft 2) AEGL-1 was based on an erroneous interpretation of text in NTP (1990) p. 35.

NTP (1990). Rats and mice were exposed to 2, 5, 10, 25, (and mice to 50) ppm TNM for 2 weeks (6 hours/day, 5 days/week). Use single 6-hour exposure for derivation.

2 ppm: None in rats or mice (rats possibly, unlikely lethargic) **[AEGL-1]**
5 ppm: None in rats; ↓ body weights, ~~**reddened lungs in mice**~~ **[AEGL-2]**
10 ppm: ↓Weight gains, lethargy in both sp.; 1 male died day 8 (treatment-related); reddened lungs in mice **[AEGL-3]**
25 ppm: All rats die on day 1 (pulm. edema); 8/10 mice die on day 3, 4 (red lungs)
50 ppm (mice only): All die on day 2 (reddened lungs)

AEGL-2 Values for Tetranitromethane				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.66 ppm	0.66 ppm	0.52 ppm	0.33 ppm	0.17 ppm

Kinkead et al. 1977. Male Sprague-Dawley CFE rats (10/dose) inhaled 10, 15, 18, 19, 21, or 23 ppm for 4 hours

Effects: Mortality: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10].

- Lethargy, slowed respiration, nose and eye irritation
- BW loss, reversible only at 10 ppm
- Early decedents had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion.
- Severity of toxicity increased with exposure concentration.
- As 10 ppm was NOEL for lethality from extreme lung irritation, and was lowest conc., MF of 3 was applied to obtain **3.3 ppm**, a conc. expected to cause only mild reversible lung irritation.

Endpoint: Mild reversible lung irritation from 4-hr exposure to 3.3 ppm

Total uncertainty factor: 10
Interspecies: 3: Key study tested most sensitive species
Intraspecies: 3: Mild reversible lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans

Modifying Factor: **3** applied to 10 ppm to obtain a concentration that would cause mild reversible lung irritation

Time Scaling: $C^n \times t = k$ (ten Berge 1986); use n=3 and n=1, except 10'=30'

AEGL-3 Values for Tetranitromethane				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
2.0	2.0	1.6	1.0	0.5

Kinkead et al. 1977. Male Sprague-Dawley CFE rats (10/dose) inhaled 10, 15, 18, 19, 21, or 23 ppm for 4 hours

Effects: Mortality: 23 ppm [10/10]; 21 ppm [10/10]; 19 ppm [6/10], 18 ppm [3/10]; 15 ppm [3/10]; 10 ppm [0/10].

- Lethargy, slowed respiration, nose and eye irritation
- BW loss, reversible only at 10 ppm
- Early decedents had moderate to severe lung congestion and hemorrhage; rats surviving the 2 weeks had mild lung congestion.
- Severity of toxicity increased with exposure concentration.
- 10 ppm was NOEL for lethality from extreme lung irritation

Endpoint: 10 ppm is NOEL for lethality from extreme lung irritation

Total Uncertainty Factor: 10
Interspecies: 3: Key study tested most sensitive species
Intraspecies: 3: NOEL for lethality from extreme lung irritation from a gas with a steep dose-response is not likely to vary greatly among humans

Modifying Factor: None

Time Scaling: as for AEGL-2 ($C^n \times t = k$; n=3 or n=1, except 10'=30')

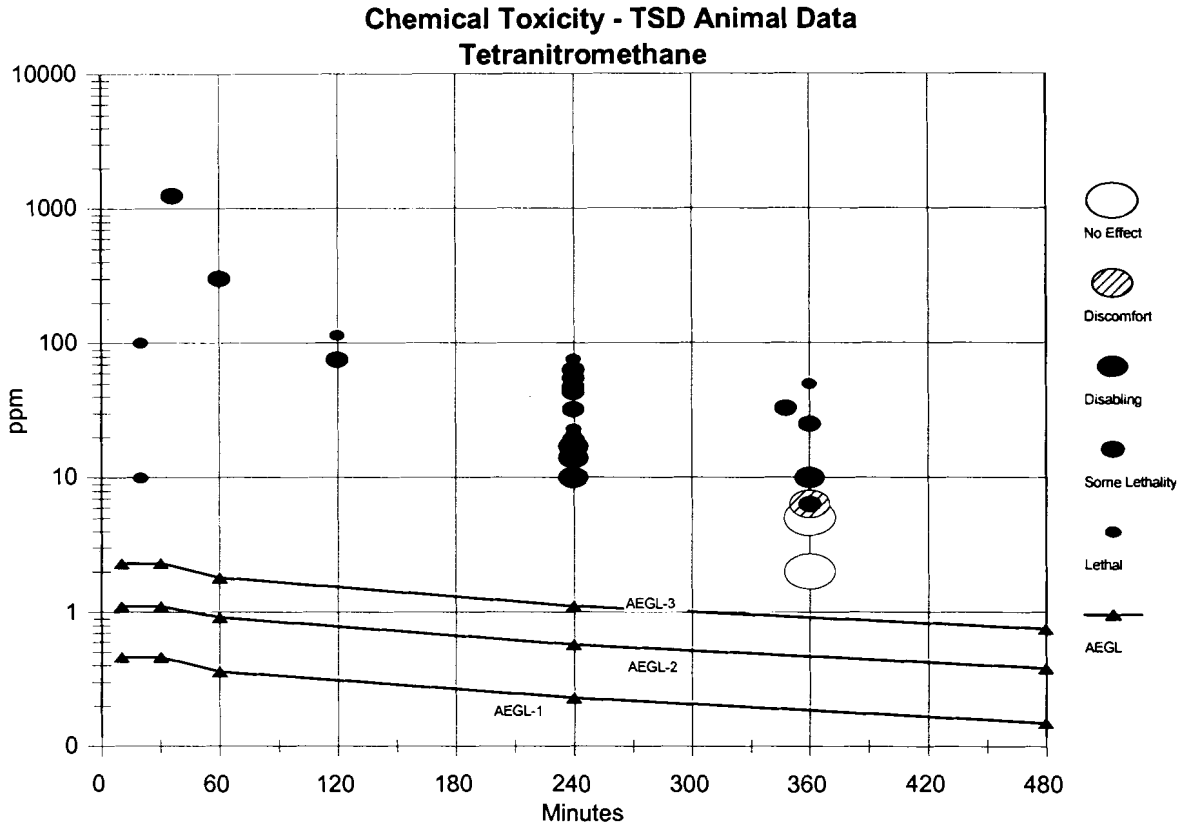
Summary of AEGL Values for Tetranitromethane (TNM)					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1[a] (Non-disabling)	**Not recommended due to insufficient data.**				
AEGL-2 (Disabling)	**0.66**	**0.66**	**0.52**	**0.33**	**0.17**
AEGL-3 (Lethal)	**2.0**	**2.0**	**1.6**	**1.0**	**0.50**

Comparison of Draft 3 (Sept '04) and Draft 2 (Oct '00) AEGL Values

Draft 3 **AEGL Values for TNM [ppm]**					
Level	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	*Not recommended due to insufficient data.*				
AEGL-2	**0.66**	**0.66**	**0.52**	**0.33**	**0.17**
AEGL-3	**2.0**	**2.0**	**1.6**	**1.0**	**0.50**

Draft 2 **AEGL Values for TNM [ppm]**					
Level	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	0.46	0.46	0.36	0.23	0.15
AEGL-2	1.1	1.1	0.91	0.57	0.38
AEGL-3	2.3	2.3	1.8	1.1	0.75

Category Plot for Tetranitromethane



Note: The above plot includes some multiple-exposure (6 hrs/d, 5 d/wk) studies: the NTP (1990) 2-wk rat and mouse studies, and the Horn 1954 six-month rat and dog studies. A single 6 hr/day exposure was input in table for these studies.

attachment 5

4/22/04

COT Comments on Propylene Oxide

Claudia M. Troxel

Jim Holler

Summary of Interim AEGL Values for PO

Level	10 m	30 m	1 h	4 h	8 h
1	110	110	60	19	11
2	1300	510	290	91	51
3	2700	1100	610	190	110

AEGL Endpoints (CMA, 1998)

- **AEGL-1** - 8-hour TWA of 31.8 ppm resulted in no worker complaints
- **AEGL-2** - Humans: Strong odor and irritation noted in monitoring study (exact nature of the irritation, other than the strong odor, was not provided, but occasional eye irritation was noted in the report as the reason for the monitoring program); average of AEGL-2 values using 4 exposure concentrations and durations

  380 ppm for 177 minutes; 525 ppm for 121 minutes; 392 ppm for 135 minutes; 460 ppm for 116 minutes
- **AEGL-3** - Highest documented human exposure concentration of 1520 ppm for 171 minutes

COT's Comments

AEGL-1:

Should consider using findings used for the AEGL-2 as basis AEGL-1 derivation. The eye irritation described by this group is an appropriate end point for AEGL-1. Time scaling should not be performed for minor/modest mucus membrane irritation associated with PO exposures.

AEGL-2:

As observations for AEGL-2 are appropriate for the AEGL-1, data on more severe irritation, port of entry cytotoxicity, and/or systemic toxicity are needed to derive AEGL-2 values.

AEGL-3:

A mouse or rat LC_{50} value should be used as the basis for derivation of AEGL-3.

AEGL-3:

Calculated BMC_{01} and $BMCL_{05}$ for mice and rats				
Species	Time (h)	BMC_{01}	$BMCL_{05}$	Reference
mouse	4	783	673	NTP, 1985
rat	4	1845	1161	NTP, 1985
rat	4	2482	2254	Jacobson, 1956
rat	4	3556	3328	Shell Oil Co., 1977

Dogs –

1363 ppm for 4 hours – 0/3 died

2005 ppm for 4 hours – 1/3 died

Considerations in selection of key study and UF for AEGL-3: PO reacts at the site of entry

Rodents are obligate nose breathers - upper respiratory tract damage. Acute exposure resulted in dyspnea, gasping, and mucous discharge from nose and/or mouth. Necropsy either didn't reveal remarkable findings, or revealed only distended stomach, correlating w/ gasping attempt to breathe by obligate nose breathers. Repeated exposures resulted in upper respiratory tract lesions, such as rhinitis and squamous metaplasia, hyperplasia, necrosis, suppurative inflammation of the upper respiratory tract epithelium

Dogs are non-obligate nose-breathers - respiratory tract damage in dogs following inhalation exposures occurred on more distal parts of the respiratory system. Gross necropsy of dogs exposed to PO concentrations up to 2481 ppm for 4 hours revealed congestion of the tracheal mucosa and lungs, spotty alveolar edema, marked perivascular and peribronchial edema, and focal areas of subepithelial edema and necrobiosis of bronchiolar epithelium.

AEGL-3, con't:

The mouse was not used because overly sensitive; ten Berge et al. 1986 noted that mice were often more sensitive than other mammals, and that "experiments using mice do not provide an appropriate basis for predicting quantitatively the mortality response in humans

Rat data: 3 different $BMCL_{05}$s (1161; 2254; 3328 ppm)

The $BMCL_{05}$ of 1161 ppm derived from the NTP (1985) study used because have the most confidence in it; this value also matches lethality no-effect-level of 1363 ppm for 4 hours for mortality in dogs, a non-obligate nose-breather

AEGL-3 based on $BMCL_{05}$ of 1161 ppm for 4 hrs; n = 1.2					
UF	10 min	30 min	1 h	4 h	8 h
3	2200	2200	1200	390	220
10	660	660	370	120	65

Intraspecies of 3 - mechanism of toxicity, irritation, not expected to differ greatly among individuals

Interspecies of 3 -

- LC_{50} values differ by ~ 3.5;
- Predicted airway/ tissue burden for mice, rats, dogs, and humans in nasal respiratory and olfactory epithelium, lung, and liver do not differ by more than 3.2;
- Measured Hb adduct levels following inhalation exposure in rats, mice, and dogs varied at most by a factor of 2.9

Lethality Bounds: **Primates**

- 0, 100, or 300 ppm for 6 hr/d, 5 d/wk for 24 months:

  2 male monkeys/group (Sprinz et al., 1982) exposed to investigate the potential neuropathological effect. The only observable differences noted between treated and controls were signs of axonal dystrophy in the medulla oblongata of the brain.

  12 cynomolgus monkeys/group (Setzer et al. (1997). No neurophysiological or neuropathological changes noted.

- No adverse effects w/ PO 7 hr/d, 5 d/wk (Rowe et al., 1956)
  1 Fe rhesus monkey exposed 154 times to 457 ppm,
  2 Fe rhesus monkeys exposed 154 times to 195 ppm,
  2 Fe rhesus monkeys exposed 154 times to 102 ppm

Humans: Highest documented human exposure conc.: 1520 ppm for 171 minutes (2.85 hours)

AEGL-3 based on $BMCL_{05}$ of 1161 ppm for 4 hrs; n = 1.2					
UF	10 min	30 min	1 h	4 h	8 h
3	2200	2200	1200	390	220
10	660	660	370	120	65

Data bounds suggest that total UF of 10 is inconsistent;

Support of interspecies UF of 1:

- data addressing *in vitro* metabolism of PO in human, rat, and mouse lung and liver microsomes indicate that human microsomal epoxide hydrolase has a greater capacity for propylene oxide metabolism than the rat and mouse epoxide hydrolase.
- The human lung cytosolic glutathione-S-transferase activity appeared to be greater than rats but less than mouse (Faller et al., 1998).

AEGL-2 derivation: Use supporting study (NTP, 1985):

Response of Mice Exposed to PO for 4 Hr			
Conc. (ppm)	Mortality		Other effects
	Males	Females	
387	0/5	1/5	Dyspnea
859	0/5	0/5	Dyspnea
1102	2/5	4/5	Dyspnea
1277	2/5	5/5	Dyspnea, sedation
2970	5/5	5/5	Dyspnea, sedation, lacrimation

No pathological changes noted at necropsy.

Dyspnea in mice most sensitive endpoint, and mice most susceptible. Although NOEL not established at this conc., no other effects were noted. In addition, the NTP study reported toxic effects occurring at much lower concentrations than those observed in other studies.

One mouse died at 387 ppm, didn't appear treatment-related:

- No females died at next higher exposure (859 ppm), while 4/5 died at 1102 ppm. Almost all other mice that died following exposure died on the first day (1 mouse died on day 2), but the 387 ppm mouse died on test day 6.
- NTP (1985) also conducted 2-wk and 13-wk study in mice:

  No mortalities in mice (5/sex/conc.) exposed to 0, 20.1, 47.2, 98.5, 196 or 487 ppm for 6 hr/d, 5 d/wk, for 2 wk. Mice at 196 and 487 ppm experienced dyspnea, and highest exposure groups were hypoactive.

  No mortalities in mice (10/sex/conc.) exposed to 0, 31, 63, 125, 250, or 500 ppm for 6 hr/d, 5 d/wk, for 13 wk except 1 male mouse in 125 ppm group on Day 14. The high concentration groups had lower bw compared to controls. Gross or microscopic pathological evaluation did not reveal any compound-related effects. Signs of toxicity were not stated, so it is unclear if none were noted, or simply not reported.

Based on the overall experimental results discussed above, the one death occurring in the female group exposed to 387 ppm for 4 hours did not appear to be consistent with treatment.

AEGL-2 Derivation

- Dyspnea in mice exposed to 387 ppm for 4 hr

Total UF of 3

- Interspecies of 1: mouse the most sensitive species, and dyspnea by far the most sensitive endpoint
- Intraspecies of 3: mechanism of toxicity, irritation, not expected to differ greatly among individuals

AEGL-2 Values (ppm)				
10 min	30 min	1 hr	4 hr	8 hr
730	730	410	130	72

AEGL-1:

COT recommends using the basis for the AEGL-2 for the AEGL-1

Humans: Strong odor and irritation noted in monitoring study (exact nature of the irritation, other than the strong odor, was not provided, but occasional eye irritation was noted in the report as reason for monitoring program); average of AEGL-2 values using 4 exposure concentrations and durations

380 ppm for 177 minutes; 525 ppm for 121 minutes; 392 ppm for 135 minutes; 460 ppm for 116 minutes

Because one does not scale across time for irritant effects, the values would be set equal across time. Therefore, one could take the average of the 4 exposures = 440 ppm. Divided by an UF of 3, the value would be 147 ppm across time

Other information:

LOA was not derived for PO in previous documents. The LOA (I=3) for PO is 21 ppm.

Summary of AEGL Values					
Level	10 min	30 min	1 hr	4 hr	8 hr
New 1	147	147	147	147	147
Old 1	110 (11)	110	60	19	11
New 2	730	730	410	130	72
Old 2	1300 (147)	510	290	91	51
New 3	2200	2200	1200	390	220
Old 3	2700	1100	610	190	110

TABLE 14. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Duration (h)	Mortality and Other Effects	Reference
Dog	2005	4	Lowest exposure concentration causing death (1/3); no mortality at 1363 ppm	Jacobson et al., 1956
Rat	4000	4	Killed 6/6	Smyth and Carpenter, 1948
Rat	4000	4	Killed 4/6	Weil et al., 1963
Rat	3448	4	Lowest exposure concentration causing death; no mortality at 2684 ppm	Jacobson et al., 1956
Rat	16,000	0.5 0.25	Death (10/10) No mortality (0/10)	Rowe et al., 1956
Rat	8000	0.5	Longest duration causing lowest number of deaths (2/10); no mortality at 0.25 h exposure	Rowe et al., 1956
Rat	4000	2.0	Longest duration causing lowest number of deaths (4/10); no mortality at 1 h exposure	Rowe et al., 1956
Rat	2970	4	Lowest experimental concentration causing death (males: 1/5; females: 2/5); no mortality at 1277 ppm	NTP, 1985
Rat (M)	4280	4	Lowest experimental concentration causing death (2/4); no mortality at 4050 ppm	Shell Oil Co., 1977
Rat (F)	4050	4	Lowest experimental concentration causing death (3/4); no mortality at 3450 ppm	Shell Oil Co., 1977
Mouse	945	4	Lowest experimental concentration causing death (lowest concentration tested)	Jacobson et al., 1956
Mouse (M)	1102	4	Lowest exposure concentration resulting in death (2/5); no mortality at 387 ppm	NTP, 1985
Mouse (F)	387 859 1102	4	Death: 1/5 (not treatment-related?) No death: 0/5 Death: 4/5	NTP, 1985
Guinea pig	16,000	1 0.5	Death: 5/5 No death: 0/5	Rowe et al., 1956
Guinea pig	8000	2	Longest duration at this concentration resulting in fewest number of deaths (1/5); no mortality at 1 h exposure	Rowe et al., 1956
Guinea pig	4000	4	Longest duration at this concentration resulting in fewest number of deaths (1/5); no mortality at 2 h exposure	Rowe et al., 1956

TABLE 15. Summary of Nonlethal Inhalation Data in Laboratory Animals

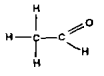
Species	Conc. (ppm)	Duration (h)	Effects	References
Dog	1363	4	Highest concentration causing no mortality; Lacrimation, salivation, nasal discharge	Jacobson et al., 1956
Rat	2684	4	Highest concentration causing no mortality; Frequent movement and preening, nasal discharge, lacrimation, salivation, gasping	Jacobson et al., 1956
Rat	1277	4	No mortality; no clinical signs or gross pathology changes	NTP, 1985
Rat (M)	4050	4	Highest concentration causing no mortality; Lacrimation, eye irritation, sedation, piloerection, mucous discharge from nose and mouth, respiratory difficulty	Shell Oil Co., 1977
Rat (F)	3450	4	Highest concentration causing no mortality; Lacrimation, eye irritation, sedation, piloerection, mucous discharge from nose and mouth, respiratory difficulty	Shell Oil Co., 1977
Rat	600	6 hr/d, 5 d/wk	Transient restless behavior observed only during first 3 days of exposure, occasional salivation and piloerection noted	Dow Chemical Company, 1981
Mouse (M)	859	4	Highest concentration causing no mortality; Dyspnea; no compound-related effects at gross necropsy	NTP, 1985
Mouse (F)	387 859	4 4	1/5 died (not treatment-related); dyspnea; no compound-related effects at gross necropsy No mortality; dyspnea; no compound-related effects at gross necropsy	NTP, 1985
Guinea pig	16,000 8000 4000 2000	0.5 1 2 7	Highest concentrations/longest durations not causing mortality; Signs of toxicity in all groups: eye and nasal irritation, breathing difficulty, drowsiness, weakness	Rowe et al., 1956

Tues 9/21/04 am.

attachment 6

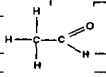
NAC/AEGL Meeting September 2004

ACETALDEHYDE



rivm

Acetaldehyde



- Colorless, highly volatile liquid
- LOA 0.56 ppm
- Metabolic intermediate in animals/humans and plants
- Natural component of food (fruit juice up to 100 mg/kg) and environment
- Produced since 1916, used as intermediate
- Human exposure mainly through metabolism of ingested alcohol

Toxicological database for acetaldehyde

HUMAN STUDIES

- No lethality data or case reports
- Experimental studies with volunteers: two old studies and six recent studies
- No occupational or epidemiologic studies

ANIMAL STUDIES

- Acute lethality data in mice, rats, hamsters, guinea pigs, rabbits and a cat
- Non-lethal toxicity in hamsters, guinea pigs, rats and mice
- Genotoxicity and carcinogenicity (hamster, rat)

AEGL-1 - Human data

- 6 recent studies on respiratory function (FEV_1)
  - healthy and asthmatic volunteers
  - 20% reduction in FEV_1 at ~ 300-700 ppm

but

  - only 2 minutes of exposure
  - exposure to aerosol instead of vapor/gas

therefore

  - These studies, although well performed, are not suitable for the purpose of developing AEGL-values for acetaldehyde

rivm

AEGL-1 - Human data

- Two old studies:

1. Silverman 1946:
   - 12 volunteers
   - 15 minutes exposure
   - nominal conc 25-50-200 ppm acetaldehyde
   - eye irritation from 50 ppm, bloodshot eyes and reddened eyelids at 200 ppm
   - most subjects were willing to work for 8 h at 200 ppm
   - some subjects objected to work at 25 ppm (reason not stated, could be related to odor)

Previous

Use for AEGL-1

rivm

AEGL-1 - Human data

2. Sim and Pattle 1957
   - 14 volunteers
   - 30 minutes exposure
   - measured concentration 134 ppm acetaldehyde
   - mild irritation of upper respiratory tract
   - no eye irritation reported for acetaldehyde (eye irr. was however reported for other tested substances)

rivm

AEGL-1

- Eye irritation relevant end-point
- 25 ppm (Silverman study) as point of departure
- UF=3 to account for variation in sensitivity which is sufficient for this direct effect
- Flatlining across time as usual for irritation

TABLE 4. AEGL-1 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
8 ppm (14 mg/m³)	8 ppm (14 mg/m³)	8 ppm (14 mg/m³)	8 ppm (14 mg/m³)	8 ppm (14 mg/m³)

rivm

Acetaldehyde | Johan Schaafsma 7

AEGL-2 - Animal data

- Two possibilities:
  1. 6-h NOEL of 1500 ppm for nasal pathology in the rat (Cassee), however:
     - No LOEL in this study
     - Severe nasal pathology only observed after repeated exposure
     - So, the 1500 ppm could be very conservative
  2. Severe dispnea in rats at 4975 ppm (no clinical signs at 2217 ppm = NOEL) during the first 30-min of 6-h exposure (28-d study), but:
     - Effect may be a reaction to odor
     - Relevance for humans questionable

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AEGL-2

- Result option 1:
  - NOEL 1500 ppm 6-h; UF 10 (3x3) => 6-h value 150 ppm
  - time scaling n=1 to longer and n=3 to shorter time points

TABLE 5. AEGL-2 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
300 ppm (900 mg/m³)	340 ppm (610 mg/m³)	270 ppm (490 mg/m³)	170 ppm (310 mg/m³)	110 ppm (200 mg/m³)

- Result option 2:
  - NOEL 2217 ppm 30-m; UF 10 (3x3) => 30-m value 220 ppm
  - effect disappears after 30-m: no time scaling

TABLE 5. AEGL-2 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
220 ppm (400 mg/m³)	220 ppm (400 mg/m³)	220 ppm (400 mg/m³)	220 ppm (400 mg/m³)	220 ppm (400 mg/m³)

rivm

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AEGL-3 - Animal data

TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Cat	4,144	4 hours	Severe toxicity	Ivanoff (1911)
Cat	13720 ppm	15 min	Death	Ivanoff (1911)
Rabbit, guinea pig, mouse	3,296	81.5 min (mouse, rabbit), 83 min (guinea pig)	death	Salem and Cullumbine (1960)
Hamster	17,000	4 hours	LC50	Kruysse et al. (1970)
Rat	20,720	30 min	LC50	Skog (1950)
Rat	16,000	8 hours	No effect	Smyth et al. (1946)
Rat	13,300	4 hours	LC50	Appelman, et al. (1982)

- dose-response information in hamster (Kruysse) and rat (Appelman)
- BMDL hamster 10640 ppm, rat 5295 ppm

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Rat lethality data - acute / subacute

- Combined data

concentration (ppm) 4 weeks exposure	concentration (ppm) 4 hours of exposure plus recovery period	number of deaths
0		0/20
401		0/20
841		0/20
2217		0/20
4975		0/20
	10436	2/10
	12673	5/10
	15683	8/10
	16801	8/10

- Same rat strain, same lab, same researchers, same report

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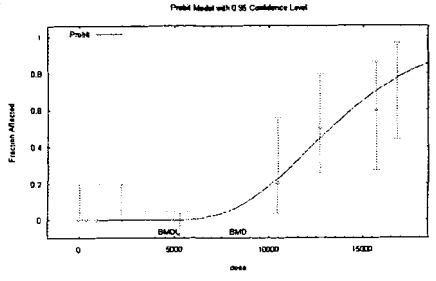
BMDL05 = 3128 - Ernie

Lethality rat - log-Probit BMDL



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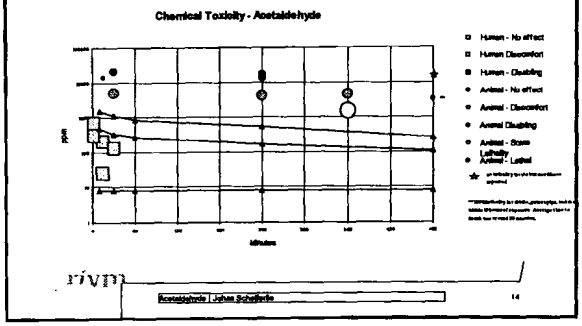
AEGL-3

- 4-h rat $BMDL_{05}$ of 5295 ppm using both the acute and subacute data of Appelman; UF=10 (3x3)
- 4 h value = 530 ppm
- time scaling n=1 to longer and n=3 to shorter time points
- If we choose option 2 for AEGL-2: flatline from 4-8 h because otherwise the 8-h value would approach the AEGL-2

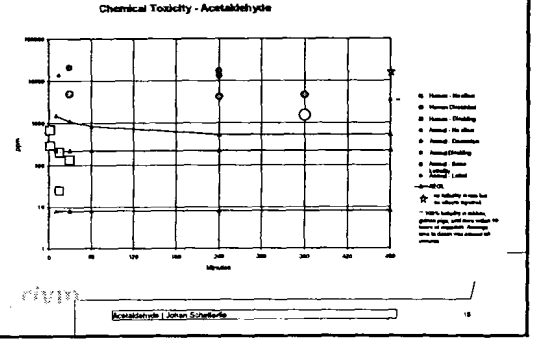
TABLE 6. AEGL-3 Values for Acetaldehyde

10-minute	30-minute	1-hour	4-hour	8-hour
1500 ppm (2700 mg/m³)	1100 ppm (2000 mg/m³)	840 ppm (1500 mg/m³)	530 ppm (950 mg/m³)	530 ppm (950 mg/m³)

Category plot (option 1 for AEGL-2)



Category plot (option 2 for AEGL-2)



Tues pm
9/21/04

Attachment 7

Vinyl Acetate

Claudia Troxel
Richard Thomas

General

- Colorless, flammable liquid with low water solubility
- Odor has been described as being immediately pleasant, but quickly becoming sharp and irritating.
  Detection odor threshold: 0.12 ppm;
  Recognition threshold: 0.4 ppm
- LOA - 0.25 ppm
- 1993 U.S. production: 2.83 billion pounds
- Main use: as a monomer in production of poly(vinyl acetate) and vinyl acetate copolymers, which in turn are used to produce water-based paints, adhesives, and other coating and binding applications.

- Metabolism: carboxylesterase;
  VA → vinyl alcohol + acetic acid
  ↓ ↑(ADH)
  acetaldehyde → acetate
- Mode of action:
  Cytotoxicity – caused by production of acetic acid; lowering of cellular pH

  DNA-protein crosslinking – caused by acetaldehyde
- Efficiently scrubbed in nasal cavity at lower concentrations, but when metabolic saturation occurs, VA makes it further down the respiratory tract

  In rats, metabolic saturation reached at ~650 ppm

Inhalation toxicity data - 2 human studies:

- Smyth and Carpenter, 1973: Controlled chamber exposure
  3-9 subjects exposed to 0.6 to 72 ppm VA for 2 - 240 min.
  effects : odor detection; eye, nose, throat irritation
  Deficiencies include no description of:
  exposure chamber
  if volunteers previously exposed or naive
  how much time lapsed between exp.

- Deese and Joyner, 1969: Notations of subjective responses to odor, eye irritation, and upper respiratory irritation recorded during air sampling of VA in workplace;
  3 individuals at each production unit;
  exposure from 0.4 to 21.6 ppm

Animal Data:

- Smyth and Carpenter, 1973:
  Lethality data in rats, mice, guinea pigs, and rabbits

  Nonlethal data in dogs: 1 dog/exposure group

- Bogdanffy et al., 1997
  Study assessed histopathology of rat nasal cavity following VA exposure for 6 h/d, 5 d/wk for 1, 5, or 20 days

- Dudek et al., 1996
  RD_{50} in mouse

TABLE 9. Summary of 4-Hour Lethal Inhalation Data in Laboratory Animals *

Species	Conc. (ppm)	Effect	Gross Necropsy of Animals That Died
General Mortality Data			
rat	1640	0/12 died	-
	3280	4/12 died (3 died during exposure)	pulmonary congestion and hemorrhage, froth in trachea, and opaque corneas
	6560	12/12 died at 90 min. of exposure	
mouse	410	0/10 died	-
	820	1/6 died (by 8 days post exposure)	pulmonary congestion, excess pleural fluid
	1640	4/6 died (during exposure)	
	3280	5/6 (during exposure)	
	6560	6/6 (during exposure)	
guinea pig	1640	0/6 died	-
	3280	1/6 died (during exposure)	pulmonary congestion and emphysema, scattered hemorrhages in the lungs
	6560	4/6 died (3 during exposure)	
	13120	6/6 died (during exposure)	
rabbit	1640	0/4 died	-
	3280	3/4 died	bloody nostrils, froth in trachea, excess pleural fluid, pulmonary hemorrhages
	6560	4/4 died (2 during exposure)	
Calculated 4-Hour LC_{50} Data			
rat	3680	LC_{50}	-
mouse	1460	LC_{50}	-
guinea pig	5210	LC_{50}	-
rabbit	2760	LC_{50}	-

* All data from Smyth and Carpenter, 1973

4

TABLE 10. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure Time	Effect	Reference
dog	51.25	4	none	Smyth and Carpenter, 1973
dog	102.5	4	none	Smyth and Carpenter, 1973
dog	205	4	blinking at 1 min., sclera red at 1 hr.	Smyth and Carpenter, 1973
dog	820	4	lacrimation at 2 min., sclera red at 4 hr.	Smyth and Carpenter, 1973
dog	1640	4	blinking and sneezing at start of exposure; lacrimation at 5 min.; eyelids inflamed at 30 min.; nasal froth at 4 hr.	Smyth and Carpenter, 1973
dog	3280	4	rubbed eyes and nose at start of exposure; tremors at 2.5 hr.; froth from nostrils at 3.5 hr.; eyes red	Smyth and Carpenter, 1973
rat	1640	4	extremities congested at 1-hr of exposure; no effect level for death (0/12)	Smyth and Carpenter, 1973
rat	600	6	degeneration and necrosis in olfactory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium	Bogdanffy et al., 1997
rat	1000	6	degeneration and necrosis in olfactory and respiratory epithelium; increase in cell proliferation in nasal respiratory and olfactory epithelium	Bogdanffy et al., 1997
mouse	410	4	no clinical signs reported; no effect level for death (0/6)	Smyth and Carpenter, 1973
mouse	380	-	RD_{50}	Dudek et al., 1996
guinea pigs	1640	4	lacrimation at 30 min; eyes and nose wet at end of exposure; no effect level for death (0/6)	Smyth and Carpenter, 1973
rabbits	1640	4	no clinical signs reported; no effect level for death (0/4)	Smyth and Carpenter, 1973

AEGL-3 – Smyth and Carpenter, 1973

Reported 4-hr lethality data in 4 species:

Guinea pigs least sensitive (LC_{50}: 5210 ppm)

Rabbit data limited to 4 animals/group (LC_{50}: 2760 pm)

Mouse overly sensitive to lethality effects (LC_{50}: 1460 ppm)

BMCLos- mouse = 226 ppm

- Rat: 12 animals/group; LC_{50} in middle range (3680 ppm)
  Therefore, rat 4-hr $BMCL_{05}$ of 1791 ppm used
- UF = 10
  interspecies: 3; lethality data for 4 species varied by factor of 3
  intraspecies: 3; mechanism of irritation
- Time scaling: default; n=3 for longer to shorter durations
  n=1 for shorter to longer (10 min = 30 min)

AEGL-3 Values for VA (ppm)				
10 min	30 min	1 h	4 h	8 h
360	360	280	180	90

AEGL-2 – Bogdanffy et al., 1997

Groups of 5 male rats/group exposed to 0, 50, 200, 600, or 1000 ppm for 6 hours to investigate effects on cell proliferation in nasal cavity;

- 0, 50, 200 ppm - no effects
- 600 ppm - degenerative lesions and increased cell proliferation in olfactory epithelium
- 1000 ppm - increased incidence/severity in olfactory epithelium lesions; some minimal lesions noted in respiratory epithelium; increased cell proliferation in olfactory epithelium

AEGL-2, con't

600 ppm for 6 hours considered a NOAEL for an AEGL-2 based on no severe histopathological effects noted after 1 day (6 hours) of exposure to either the olfactory or respiratory epithelium and moderate effects noted in only one rat in one of five cross sections. Although it is not clear if these effects were only "degenerative" without necrosis at the 600 ppm concentration, it can be assumed that these effects are reversible since they were not severe nor was it mentioned that there was necrosis in the 1 day exposure group. Further, severe lesions were observed in only 1 rat at cross section level II in the 600 ppm 5-day exposed rats. This "localized" lesion (only at level II) in one of five rats would also suggest that the lesions are only degenerative and reversible.

AEGL-2, con't

- Endpoint: 600 ppm for 6 hours
- UF – 10

  Interspecies: 3

  Intraspecies: 3

  A higher UF is unjustified because that would reduce the AEGL-2 values to concentrations that did not result in serious health effects in human volunteer studies (for example, an UF of 30 would drive the 8-hour AEGL-2 to 15 ppm).
- Time scaling - default; n=3 for longer to shorter durations

  n=1 for shorter to longer (10 min = 30 min)

AEGL-2 Values for VA (ppm)				
10 min	30 min	1 h	4 h	8 h
140	140	110	69	45

AEGL-1 – Smyth and Carpenter, 1973

ppm.	n	min	Response
0.6	9	2	none
1.3	9	2	9 immediate odor; 5 no odor at 2 min.
4	9	2	9 immediate odor, 3 no odor at 2 min 1 minimal eye, nose, and throat irritation
8	9	2	9 immediate odor, 1 no odor at 2 min 2 minimal eye, nose, and throat irritation
20	9	2	9 immediate odor, 1 minimal eye, nose, and throat irritation
≥ 20	3	240	3 complete olfactory fatigue in 3-116 min. 1 persistent slight throat irritation
34	3	120	1 complete, 2 partial olfactory fatigue 1 transient, 1 persistent throat irritation
72	4	30	4 strong odor, partial olfactory fatigue 4 slight throat irritation 20-60 min. after exp; eye irritation to 60 min. after exposure; subjects expressed unwillingness to work at this conc. for 8 hrs

B

13 ppm

67 ppm

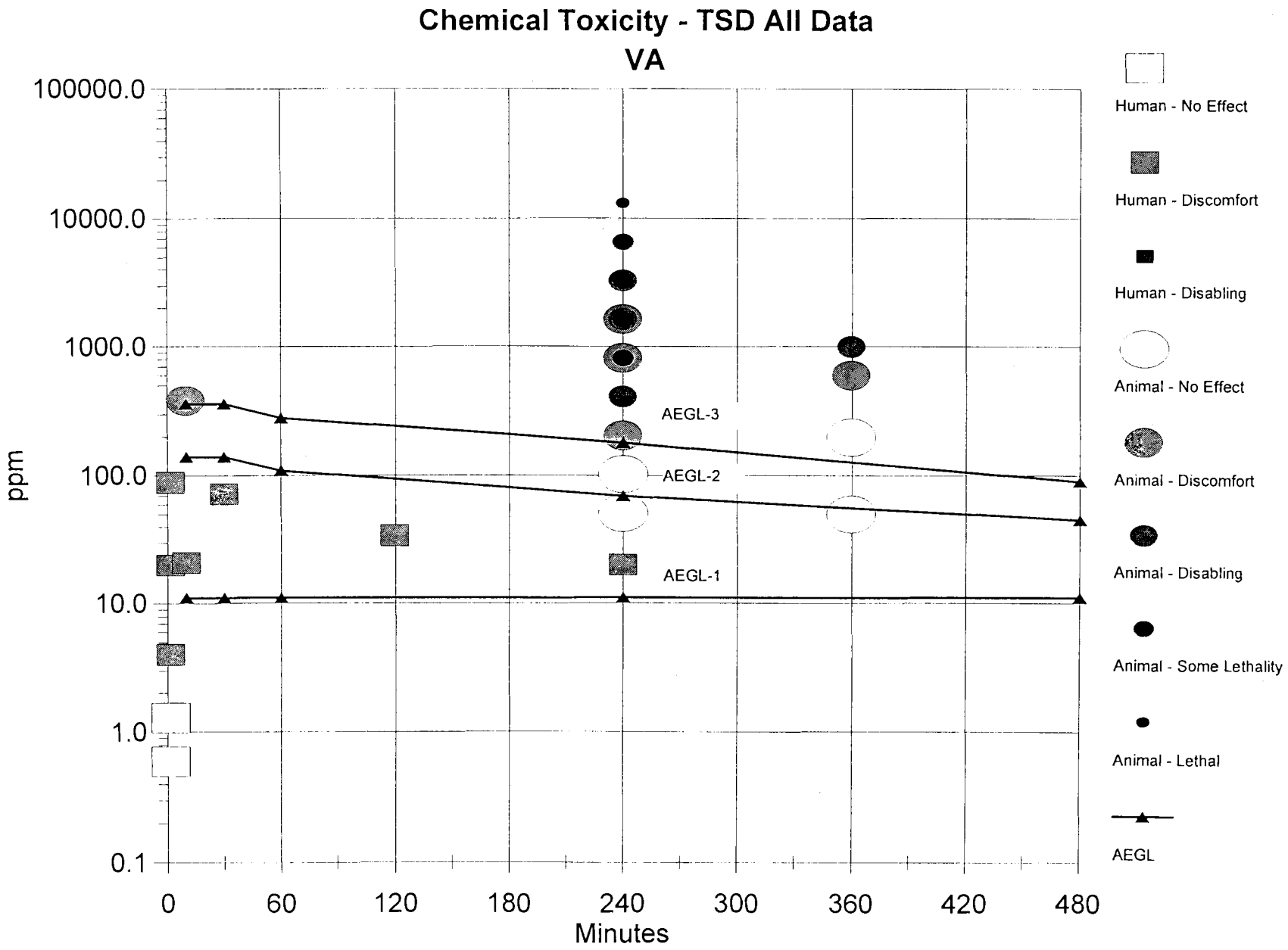
AEGL-1, con't

- Endpoint: Human exposure to 34 ppm for 2 hrs - 1/3 individuals complained of persistent throat irritation, while exposure to 72 ppm for 4 hr resulted in irritation severe enough that the exposed subjects expressed an unwillingness to work at this concentration for 8 hours. Therefore, exposure to 34 ppm for 2 hours represents a no-effect level for notable discomfort.
- UF: 3
  interspecies: 1
  intraspecies: 3; irritation local effect of chemical, not expected to vary greatly among individuals
- Time scaling: value set equal across time because irritation considered a threshold effects and should not vary across time

AEGL-1 Values for VA (ppm)				
10 min	30 min	1 h	4 h	8 h
11	11	11	11	11

Summary of Proposed AEGL Values

Level	10 m	30 m	1 hr	4 hr	8 hr	Endpoint
1	11	11	11	11	11	34 ppm for 2 hr: no-effect level for notable discomfort
2	140	140	110	69	45	NOEL for severe histopathological effects in rats at 600 ppm for 6 hr
3	360	360	280	180	90	Threshold for lethality: 4-hr $BMCL_{05}$ of 1791 ppm in rats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10000.0
1000.0
100.0
10.0
1.0
0.1
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

Sept 22, 2004

Attachment 8

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFUR CHLORIDE (CAS NO. 10025-67-9)

PRESENTED BY

KOWETHA DAVIDSON
Oak Ridge National Laboratory

CHEMICAL MANAGER
ERNEST FALKE
U.S. EPA

NAC/AEGL MEETING, Washington, DC
SEPTEMBER 21-23, 2004

1

SULFUR CHLORIDE
CAS NO. 10025-67-9

COMMON SYNONYMS:
Sulfur monochloride, disulfur dichloride

PHYSICAL CHARACTERISTICS:

- Light amber to yellowish red, fuming, oily liquid
- Vapor pressure: 6.7 torr @ 20°C
- Vapor density: 4.66 (air = 1)
- Soluble in organic solvents
- Conversion: 1 ppm = 0.181 mg/m3

2

DESCRIPTION

- Decomposes primarily to hydrogen chloride, sulfur dioxide, and sulfur in water or moist environment
- ODOR: irritating, suffocating, penetrating, nauseating
- ODOR DETECTION THRESHOLD: No data

3

HUMAN DATA

- Irritation threshold: 2-66 ppm
- Considered an upper respiratory tract irritant in humans
- Upper respiratory tract irritation may be due to decomposition products

4

ANIMAL DATA

Bomhard et al., 2000

- **Study type:** 4-hour inhalation
- **Species/Strain:** rat/strain not reported
- **Sex:** males and females (5 of each sex/group)
- **Observation period:** 14 days
- **Endpoints:** clinical signs, body weight, mortality, gross pathologic changes

5

Results

1.45 ppm	no effects
33.3 ppm	no effects
242 ppm	bloody and serous nasal discharge, breathing difficulty, piloerection, reduced activity, and ungroomed fur (signs of discomfort)
312 ppm	same as 242 ppm but probably more severe, no deaths

6

Results (Cont.)

453 ppm: 3/10 died, breathing difficulty, cyanosis, corneal opacity, necrosis in the nose; emphysema, pulmonary edema, effects in liver and spleen, gastrointestinal irritation.

519 ppm: 6/10 died; other effects same as described above

997 ppm: 10/10 died; other effects same as described above

7

AEGL -1 VALUES

10 min	30 min	1 hour	4 hour	8 hour
0.67 ppm [3.7 mg/m3]	0.67 ppm [3.7 mg/m3]	0.67 ppm [3.7 mg/m3]	0.67 ppm [3.7 mg/m3]	0.67 ppm [3.7 mg/m3]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: NOEL for upper respiratory irritation, breathing difficulty, signs of discomfort in rats exposed to 33.3 ppm for 4 hours				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 1				
Time Scaling: $C^n H t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

8

AEGL -2 VALUES

10 min	30 min	1 hour	4 hour	8 hour
2.4 ppm [27 mg/m3]	2.4 ppm [27 mg/m3]	1.9 ppm [10 mg/m3]	1.2 ppm [6.6 mg/m3]	0.61 ppm [3.4 mg/m3]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: Upper respiratory irritation, breathing difficulty, signs of discomfort in rats exposed to 242 ppm for 4 hours				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 2				
Time Scaling: $C^n H t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

9

AEGL -3 VALUES

10 min	30 min	1 hour	4 hour	8 hour
6.6 ppm [36 mg/m^3]	6.6 ppm [36 mg/m^3]	5.2 ppm [29 mg/m^3]	3.3 ppm [18 mg/m^3]	1.6 ppm [8.8 mg/m^3]
Key Reference: Bomhard, E.; Loser, E., and Pauluhn, J. 2000. Acute toxicologic evaluation of disulfur dichloride. Int. J. Toxicol. 19: 342.				
Endpoint/Concentration/Rationale: $BMLD_{05}$ = 328 ppm) for a 4-hour exposure;. 288				
Uncertainty Factors/Rationale: Total uncertainty factor: 100 (default) Interspecies: 10 (default) Intraspecies: 10 (default)				
Modifying Factor: 1				
Time Scaling: $C^n H t = k$, n = 3 and n = 1 when scaling to shorter and longer durations, respectively (default)				

10

DATA ADEQUACY FOR SULFUR CHLORIDE

Only one acute inhalation study was available for deriving AEGLs.

The study showed clear concentration-response relationships for lethal and non-lethal effects.

AEGL values were based on analytical concentrations; decomposition products were not an issue during exposure

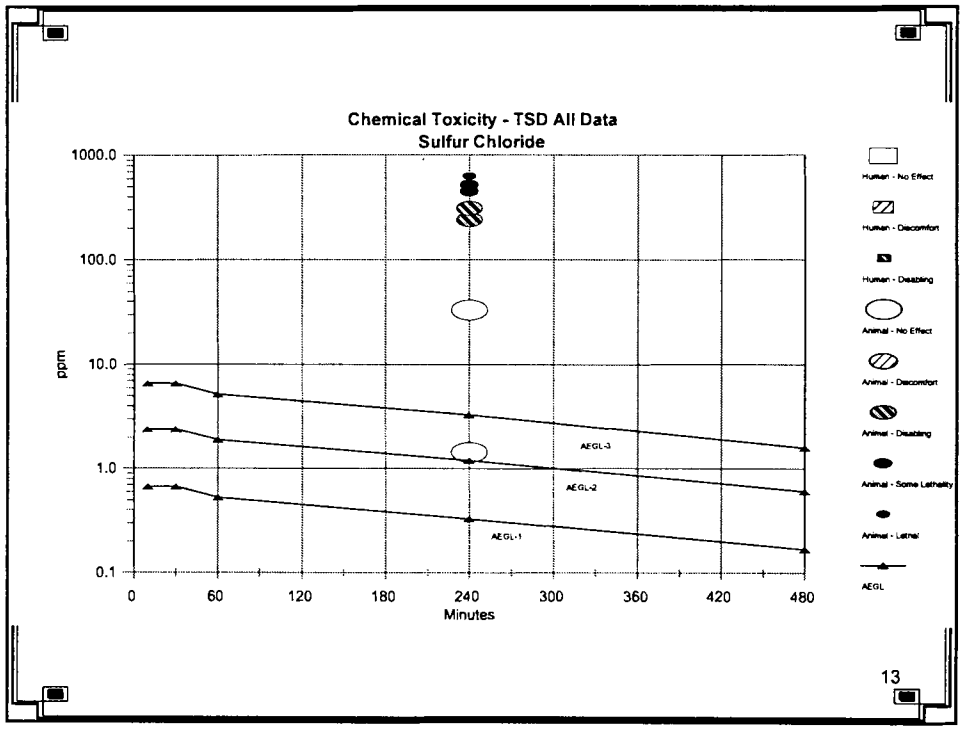
Default uncertainty factors were used in acknowledgment of the lack of additional data.

11

Proposed AEGL Values For Sulfur Chloride (ppm [mg/m^3])

Classification	10 min	30 min	1 hour	4 hour	8 hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.67 [3.7]	0.67 [3.7]	0.53 [2.9]	0.33 [1.8]	0.17 [0.94]	No effect level (Bomhard et al., 2000)
AEGL-2 (Disabling)	2.4 [13]	2.4 [13]	1.9 [10]	1.2 [6.6]	0.61 [3.4]	Upper respiratory tract irritation and breathing difficulty (Bomhard et al., 2000)
AEGL-3 (Lethal)	6.6 [36]	6.6 [36]	5.2 [29]	3.3 [18]	1.6 [8.8]	BMDL$_{05}$ for lethality (Bomhard et al., 2000)

12


Chemical Toxicity - TSD All Data
Sulfur Chloride
1000.0
100.0
10.0
1.0
0.1
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL
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Attachment 9

ACUTE EXPOSURE GUIDELINE LEVELS FOR DIBROMOETHANE (CAS NO. 10025-67-9)

PRESENTED BY
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NAC/AEGL MEETING, Washington, DC
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DIBROMOETHANE

CAS NO. 106-93-4

COMMON SYNONYMS: Ethylene dibromide; EDB

PHYSICAL CHARACTERISTICS:

- heavy colorless liquid
- Vapor pressure: 11 mm Hg at 25°C; 17.4 mm HG at 30°C
- Vapor density: 6.5 (air = 1)
- Soluble in ethanol and ethyl ether
- Conversion: 1 ppm = 0.13 mg/m^3

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OTHER INFORMATION

- **Past use:** scavenger in leaded gasoline and as an agricultural fumigant
- **Current use:** chemical intermediate for pharmaceuticals, dyes, polymers, and other chemicals
- **ODOR:** chloroform-like, foul, pungent, or sweetish
- **ODOR DETECTION THRESHOLD:** 10 ppm

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HUMAN DATA

- Effects at lethal concentrations
  - Irritating to eyes, throat and respiratory tract
  - Diarrhea
  - CNS effects: restlessness, nervousness, combativeness, lethargy
  - Pulmonary edema
  - Hepatomegaly, degenerative changes in the liver
  - Liver and renal failure
  - Congestion of the viscera and brain
  - Elevated blood and tissue bromine levels

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HUMAN DATA

- Effects at Non-lethal Concentrations
  - Irritation to the eyes (conjunctiva, eyelids)
  - Respiratory tract irritation (75 ppm?)
  - Fatigue, loss of appetite, headache, and depression
  - Gastrointestinal discomfort and vomiting (100-200 ppm?)
  - No clear exposure-response data

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ANIMAL DATA

Lethality Data (Single Inhalation Exposure)

Clinical signs and gross and microscopic findings

- **Dog:** 1 hour exposure to 1, 2, or 5 mL DBE vaporized in a 100-L Chamber
- **Effects**: evidence of eye (conjunctivitis, corneal opacity) and respiratory tract irritation (rales, rattling, labored breathing, pulmonary hemorrhage, bronchopneumonic foci ; CNS effects (restlessness, clonic twitching, strong salivation); brain and intestinal hemorrhage, liver damage; death within 12-18 hours after 2 or 5 mL or 3 weeks after 1 mL

- **Rat:** 200-10,000 ppm for 1.2 minutes to 16 hours
- **Effect**: weight loss, irritability, unkempt appearance, respiratory tract irritation (bloody discharge from the nose, pulmonary congestion, edema, hemorrhage, and inflammation, liver damage (cloudy swelling, fatty degeneration and necrosis), kidney damage (interstitial congestion, edema, cloudy swelling of tubular epithelium)

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ANIMAL DATA (Cont.)

Lethality Data (Single Inhalation Exposure)

Clinical signs and gross and microscopic findings

- **Guinea Pig:** 2000-8000 ppm for 30-150 minutes
- **Effects:** upper respiratory tract irritation, generalized weakness, damage to the kidney, pancreas, spleen, heart, liver, and adrenals; swelling and interstitial edematous degeneration of the abdominal vascular system; death within 18 hours

- **Rabbit:** Unknown conc. (induced light anesthesia) for 10 minutes
- **Effects:** evidence of respiratory tract irritation (rapid breathing and snuffling, enlarged lungs filled with frothy exudate), evidence of vascular congestion and cyanosis, liver damage (enlarged and mottled, fatty change, marked congestion); death within 18 hours

Similar effects were observed in animals exposed repeatedly to DBE

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Acute exposure of rats to 1,2-dibromoethane

Concentration (ppm)	Duration of exposure	Mortality	% lethality	Lethal times[a] (LCt)
10,000	6.0 min	20/20	100	$LCt_{99.99}$ = 9 min
	4.2 min	7/10	70	LCt_{50} = 2.4 min
	3.0 min	2/4	50	LCt_{01} = 0.6 min
	1.8 min	1/20	5	
	1.2 min	0/20	0	
5000	8.4 min	20/20	100	$LCt_{99.99}$ = 21 min
	6.0 min	9/10	90	LCt_{50} = 5.4 min
	4.2 min	5/15	33	LCt_{01} = 1.8 min
	3.0 min	3/30	10	
	2.4 min	0/20	0	
3000	12 min	5/10	50	$LCt_{99.99}$ = 36 min
	6 min	0/20	0	LCt_{50} = 10.8 min
				LCt_{01} = 3.6 min
1600	30 min	20/20	100	$LCt_{99.99}$ = 66 min
	24 min	12/15	80	LCt_{50} = 18 min
	18min	4/15	27	LCt_{01} = 6 min
	12 min	0/30	0	
800	48 min	13/20	65	$LCt_{99.99}$ = 132 min
	32.8 min	10/20	50	LCt_{50} = 45 min
	30 min	4/20	20	LCt_{01} = 16.8 min
	24 min	4/20	20	

Source: Rowe et al., 1952

[a]Calculated by NIOSH 1977a.

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Acute exposure of rats to 1,2-dibromoethane				
Concentration (ppm)	**Duration of Exposure**	**Mortality**	**% Lethality**	**Lethal times[a] (LCt)**
400	5.0 h	20/20	200	$LCt_{99.99}$ = 7.50 h
	3.0 h	17/20	85	LCt_{50} = 2.00 h
	2.5 h	19/20	95	LCt_{01} = 0.62 h
	2.0 h	16/20	80	
	1.4 h	5/25	25	
	1.0 h	2/20	10	
	48 min	1/20	5	
	36 min	0/20	0	
200	16.0 h	19/20	95	$LCt_{99.99}$ = 42 h
	12.0 h	10/20	50	LCt_{50} = 12 h
	8.5 h	9/20	45	LCt_{01} = 2 h
	7.0 h	4/11	36	
	5.0 h	3/10	33	
	4.0 h	0/5	0	
	3.0 h	1/11	9	
	2.0 h	0/5	0	
	1.4 h	0/20	0	
100	8.5 h	0/20	0	
	12.0 h	0/20	0	
	16.0 h	0/20	0	

Source: Rowe et al., 1952

aCalculated by NIOSH 1977a.

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Acute exposure of guinea pigs to 1,2-dibromoethane				
Concentration (ppm)	**Duration of exposure**	**Mortality**	**% lethality**	**Lethal times[a] (LCt)**
400	7.0 h	20/20	100	Not calculated by NIOSH
	5.0 h	18/20	90	
	3.0 h	5/10	50	
	2.0 h	0/20	0	
200	7.0	0/15	0	

Source: Rowe et al., 1952

aCalculated by NIOSH 1977a.

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ANIMAL DATA

Non-Lethal Data (Single Inhalation Exposure)

Clinical signs and gross and microscopic findings

- **No studies on non-lethal toxicity after a single exposure**
- **Non-lethal targets and effects were similar to those of single lethal concentrations**

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Summary of Nonlethal Effects of Inhaled 1,2-dibromoethane Vapor in Experimental Animals

Species/Strain/ Sex	Expt. Protocol	Effects/Comments	Reference
Rats/	100 ppm, 8.5, 12.0, & 16.0 ppm	No effects observed	Rowe et al. 1952
Rat/F344/ M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	**Systemic:** dec. wt. gain 15 (M) & 75 ppm (M/F; adrenal cortical and thyroid follicular lesions (F); **Nasal cavity:** no effect at 3 ppm lesions (cytomegaly, hyperplasia, metaplasia, cilia loss) at15 & 75 ppm	NTP 1982; Reznik et al. 1980,
Rat/F344/ M&F	0, 3, 10, 40 ppm, 6 h/d, 5 d/wk, 13 wks	**Systemic:** mild liver lesions at 40 ppm Nasal cavity: hyperplasia & single cell necrosis at 10 ppm and also squamous metaplasia at 40 ppm; no effect at 3 ppm	Nitschke et al. 1980, 1981

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Summary of Nonlethal Effects of Inhaled 1,2-dibromoethane Vapor in Experimental Animals			
Mice/B6C3F$_1$/ M&F	0, 3, 15, 75 ppm, 6 h/d, 5 d/wk, 13 wks	**Systemic:** dec. wt. gain 3 (F), 15 & 75 ppm (M&F) **Nasal cavity:** no effect at 3 or 15 ppm; lesions (cytomegaly, hyperplasia, squamous metaplasia, cilia loss at 75 ppm; **other effects**: eye irritation and megalocytes in bronchioles at 75 ppm	NTP 1982; Reznik, 1980
Guinea pigs/M&F	200 ppm for 7 h	no effects observed	Rowe et al., 1952
Guinea pigs/M&F	50 ppm, 7 h/d. 57 exposures in 80 d	growth depression, inc. liver, lung, kidney wt., microscopic lesions in liver & kidney	Rowe et al 1952
Guinea pigs/M&F	25 ppm, 7 h/d, 13 exposures in 17 d & 145 exposures in 205 d	no effects observed	Rowe et al. 1952

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Summary of Developmental Effects of Inhaled 1,2-dibromoethane Vapor in Experimental Animals			
Rats/Long-Evans/F	0, 0.43, 6.67, or 66.67 ppm, 4 h/d, 3 d/wk, GD 3-20	**Maternal:** no effect on maternal behavior; ↑ defecation; ↓ weight gain **Offspring:** no adverse effect on various neurotoxicity test performed on day 30, 63, 78, 83, 95, and 100	Smith and Goldman, 1983
Rats/F	65 ppm for 6 h/d or 130 ppm for 3 h/day, GD 10, 11, 12	**Maternal:** transient toxicity (not described) at 130 ppm **Offspring: 130 ppm:** ↑fetal death and spontaneous activity; **65 ppm:** ↓exploratory activity, peak night activity, index of neurobehavorial development (postnatal day 11); behavior affected up to week 8 of age	Vodickova et al., 2003
Rat/CD/F	20, 38, 80 ppm, 23 h/d, GD 6-15	**Maternal:** 50% deaths at 80 ppm; no live litters; wt. loss or ↓ wt. gain at 20 & 38 ppm **Fetal:** no live fetuses at 80 ppm; ↓ fetal wt. at 38 ppm; no effect at 20 ppm	Short et al., 1978
Mouse/CD-1/F	20, 38, 80 ppm, 23 h/d, GD 6-15	Maternal: 100% deaths at 80 ppm; 4 deaths at 38 ppm, ↓ wt. gain and fd consumption at 20 and 38 ppm **Fetal:** ↓ no. viable fetuses, live litters; and fetal wt. & ↑ incidence of soft tissue & skeletal abnormalities at 38 ppm; ↓ fetal wt. & skeletal abnormalities at 20 ppm	Short et al., 1978

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Genetic Toxicity & Carcinogenicity

- Genetic Toxicity
  - No genetic toxicity studies in animals exposed by inhalation
  - DBE is genotoxic in the liver and testicular germ cells of mice and rats treated in vivo
  - In in vitro systems, DBE is genotoxic in bacteria (not in glutathione deficient Salmonella strains), fungi, Drosophila, and cultured mammalian cells; exogenous metabolic activation is not required
- Carcinogenicity
  - **Rats:** **≥10 ppm**, 6 h/day for 88 to 104 wks: nasal cavity tumors, mesotheliomas (tunica vaginalis), mammary gland fibroadenomas; **≥20 ppm** 6 h/d, 18 months: hemangiosarcomas, pheochromocytoma & cortical adenoma/carcinoma in the adrenal gland; subcutaneous mesenchymal tumors; **40 ppm**, 6 h/d, 91-104 wks: lung alveolar-bronchiolar adenoma/carcinoma
  - **Mouse:** **≥ 10 ppm**, 6 h/d, 90-104 wks: respiratory tract (bronchus, bronchiole, lungs) multiple tumor types, hemangiosarcoma, mammary adenocarcinoma (females); **20 ppm**, 6 h/d, 6 months: lung adenoma; **40 ppm**, 6 h/d, 78-104 wks: lung alveolar, bronchiolar adenoma/carcinoma (males in 78 wks); nasal cavity adenoma/carcinoma (females)

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Metabolism & Disposition

- DBE is metabolized by two pathways
  - Microsomal oxidation via cytochrome P450 pathway metabolites
    - CYP2E1 most reactive isoenzyme
    - Produces protein reactive
    - Responsible for tissue toxicity
    - Accounts for 15-27% of the metabolic activity in the rat
  - Glutathione conjugation via glutathione-S-transferase pathway
    - Produces DNA reactive metabolites
    - Isoenzymes activity range from fast and slow activity
    - Responsible for genotoxicity and carcinogenicity
    - Accounts for about 85% of the metabolic activity in the rat
- PBPK Model
  - Rats have much higher (about three times) predicted blood concentrations of DBE than humans after an 8-hour exposure to 40 ppm
  - Production of P450 & GSH metabolites approximately equal in humans
  - Rat produces about four times more P459 metabolites than most sensitive human and about 80 times more GSH metabolites
  - About twofold difference in production of P450 metabolites in humans with high & low P450 activity
  - About a 10-fold difference in production of GSH metabolites in humans with high & low GSH activity

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Susceptible Populations

- Individuals undergoing disulfiram (antabuse) treatment for alcohol abuse may be more sensitive to effects of DBE.
- Genetic polymorphism of the P450 and GSH enzyme systems contribute to variability in the population.

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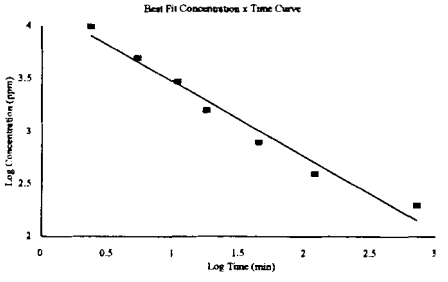
Concentration-Exposure Duration Relationship

Time	Conc.	Log Time	Log Conc.
2.4	10,000	0.38	4.00
504	5,000	0.73	3.70
10.8	3,000	1.03	3.48
18.0	1,600	1.26	3.20
45.0	800	1.65	2.90
120.0	400	2.08	2.60
720.0	200	2.86	2.30



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AEGL -1 VALUES

10 min	30 min	1 hour	4 hour	8 hour
No values were derived				

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AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
84 ppm	**38 ppm**	**23 ppm**	**8.7 ppm**	**5.3 ppm**
Key Reference: Vodickova et al 2003				
Test Species/Strain/Number: pregnant rats; strain and number exposed was not reported				
Exposure Route/Concentrations/Durations: inhalation, 65 ppm for 6 hour or 130 ppm for 3 hours daily on GD 10, 11, and 12				
Effects: 130 ppm: transient maternal toxicity; dead fetuses, low birth weight, high level of spontaneous activity 65 ppm: low birth weight; evidence of developmental neurotoxicity (lower exploratory and night activity, and lower index of neurobehavioral development on day 11				
Endpoint/Concentration/Rationale: developmental neurotoxicity at 65 ppm, 6 hour/day on GD 10, 11, 12; developmental neurotoxicity is considered an acute effect although exposure was on 3 consecutive days				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 1 PBPK modeling indicate that rats may be 4-80 times more sensitive than humans; effects are similar between animals and humans indicating similar pharmacodynamics Intraspecies: 10 PBPK modeling indicate that humans vary by a factor of about 10 in the production of reactive metabolites., and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: $C^n \times t = k$, where n = 1.4 based on regression of LC_{50} values for exposure duration ranging from 2.4 minutes to 12 hours.				
Data Adequacy: The study used to derive AEGL-2 values were derived from an abstract, which did contained few details. The rats were exposed to only one concentration for the 6-hour duration				

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AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
166 ppm	**77 ppm**	**46 ppm**	**46 ppm**	**46 ppm**
Key Reference: Rowe et al. 1952				
Test Species/Strain/Number: rat/strain was not reported/4-20 animals/group				
Exposure Route/Concentrations/Durations: inhalation/100-10,000 ppm for 1.2 minutes to 16 hours				
Effects: death occurred at all exposure concentrations but not all exposure durations. Deaths within the first 24 hours was attributed to cardiac and respiratory failure, later deaths were attributed to secondary pneumonia. Rats that died lost weight, showed evidence of upper and lower respiratory tract irritation. Microscopic findings included severe pulmonary damage, degeneration and necrosis in the liver, and congestion and edema in the kidney tubules 16-24 hours after exposure. Specific concentrations were not provided.				
Endpoint/Concentration/Rationale: concentration causing no lethality				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 1 PBPK modeling indicate that rats may be 4-80 times more sensitive than humans; effects are similar between animals and humans indicating similar pharmacodynamics Intraspecies: 10 PBPK modeling indicate that humans vary by a factor of about 10 in the production of reactive metabolites., and human taking therapeutic doses of disulfiram could have an increased sensitivity to 1,2-dibromoethane.				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: $C^n \times t = k$, where n = 1.4 based on regression of LC_{50} values for exposure duration ranging from 2.4 minutes to 12 hours.				
Data Adequacy: A very detailed acute inhalation exposure study was available with exposure concentrations ranging from 200 to 10,000 ppm and exposure duration ranging from 0.6 minutes to 16 hours. LCt values were calculated for each exposure concentration.				

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TABLE 7. Summary of AEGL Values [ppm (mg/m^3)]

Classif.	Exposure Duration					
	10 min	**30 min**	**1 hour**	**4 hour**	**8 hour**	**Endpoint/Ref.**
AEGL-1 (Nondisabling)	No data to derive values					
AEGL-2 (Disabling)	84 (646)	38 (292)	23 (177)	8.7 (67)	5.3 (41)	Developmental neurotoxicity (Vodickova et al., 2003
AEGL-3 (Lethal)	166 (1277)	76 (585)	46 (354)	17 (131)	10 (77)	no effect level for lethality (Rowe et al. 1952)

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Attachment 10

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

HYDROXYLAMINE (CAS Reg. No. 7803-49-8)

H_2N-OH

ORNL Staff Scientist: Sylvia Milanez

Chemical Manager: George Cushmac

Chemical Reviewer: Lynn M. Beasley

INTRODUCTION

- Hydroxylamine (HA) is a very unstable, explosive, and hygroscopic solid that is sold as a ≤50% aqueous solution. It decomposes in air at ambient conditions (in the presence of CO_2 and H_2O) to form ammonia, nitrogen, and dinitrogen monoxide.

- HA is a normal cellular metabolite formed the enzymatic reduction of nitrates or nitrites, or by the oxidation of ammonia. HA is reduced to ammonia by hydroxylamine reductase, which is present in all mammals.

- HA is a dermal sensitizer and causes hemolytic anemia (shown in man, mouse, rat, rabbit, and cat) when administered orally or intravenously. Effects include altered hematology parameters, Heinz body formation, splenomegaly, sulfhemoglobinemia, methemoglobinemia, and anticoagulant effects.

- At near-lethal doses, motor excitability and convulsions are seen, which are likely a secondary effect of hypoxia due to methemoglobin formation.

- No odor thresholds were found for HA. A chemical company has a workplace exposure guidance level of 0.1 mg/m^3 based on a 2-year drinking water study (BASF 2004a).

ANIMAL NON- INHALATION TOXICITY DATA

- **Acute Lethality:** ***No acute lethality inhalation studies were located.***

- LD_{50} values for HA free base and/or its Na and HCl salts were reported by the oral, intraperitoneal, and/or subcutaneous routes in rats, mice, dogs, and guinea pigs.

- Toxic effects included: dyspnea, apathy, slight cyanosis, prostration, staggering, tonic convulsions, hemolytic anemia (decreased RBC and hematocrit, increased reticulocytes), and methemoglobinemia. Necropsy revealed heart and lung hyperemia, discoloration of the lungs, liver, and kidneys, and liver texture changes.

ANIMAL INHALATION TOXICITY DATA

- **Nonlethal Toxicity:** Inhalation by rats of air "enriched with the possibly volatile components" of HA-sulfate or of "an atmosphere saturated with vapor" of HA-sulfate for 7-8 hrs caused no clinical signs, death, or pathological abnormalities during 14-day observation period (BASF 2004).

- No mortality or toxicity occurred in rats exposed for 1 hr to a "fog" of atomized HA-sulfate or HA-HCl saturated solutions (Angus Chem. Co. 1984).

- Rats or dogs exposed to 33, 100, or 300 mg/m^3 aerosolized HA-nitrate for 90 days (6 hrs/day) had hemosiderosis of the spleen, liver, and kidney, rhinitis, dermatitis, tracheitis and occasional bronchopneumonia

- Guinea pigs dermally sensitized to HA-sulfate exposed for 30 min to 6.5 or 13.2 mg/m^3 HS aerosol had no changes in their breathing rates. [Study concludes that exposure caused neither pulmonary sensitization nor sensory irritation.]

DERIVATION of AEGL VALUES FOR HYDROXYLAMINE

- Due to the lack of adequate data, AEGL-1, AEGL-2, and AEGL-3 values were not proposed.

Summary of AEGL Values for Hydroxylamine						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1[a] (Non-disabling)	Not proposed due to insufficient data.					
AEGL–2 (Disabling)						
AEGL–3 (Lethal)						

AMMONIA AEGL-2 AND AEGL-2 VALUES AND RATIONALE

A suggestion has been made that the irritancy of HA could be assumed to be at worst case equal to that of ammonia. Therefore, ammonia AEGL values based on irritancy could possibly be used set AEGL-1 and/or AEGL-2 values.

FOR AMMONIA

AEGL-1 was based on 2/6 humans experiencing faint irritation after exposure to 30 ppm ammonia for 10 min (MacEwen et al., 1970). UF =1; time scaling not applied because upper respiratory tract irritation at low ammonia concentrations is not expected to become more severe with duration of exposure; adaptation occurs during prolonged exposure to ammonia.

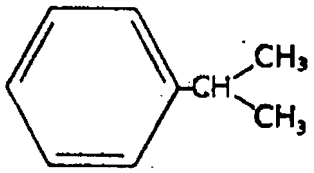
AEGL-2 was based on "offensive" irritation to eyes and respiratory tract of nonexpert human subjects exposed to 110 ppm ammonia for 1 hr, but at next higher concentration, some reported effects were unbearable and left the chamber. UF=1; $C^2 \times t = k$, was used to extrapolate to 5, 10, and 30 min. The same AEGL-2 values were established for 1-8 hrs, because the responses at 110 ppm were similar after exposure for 1 and 2 hrs.

SUMMARY OF AEGL VALUES FOR AMMONIA [ppm (mg/m^3)]							
Classification	**Exposure Duration**						**Endpoint (Reference)**
	5'	**10'**	**30'**	**1 hr**	**4 hrs**	**8 hrs**	
AEGL-1 (Nondisabling)	30	30	30	30	30	30	Mild irritation (MacEwen et al., 1970)
AEGL-2 (Disabling)	380	270	160	110	110	110	Irritation: eyes and throat; urge to cough (Verberk, 1977)
AEGL-3 (Lethal)	3800	2700	1600	1100	550	390	Lethality (Kapeghian et al., 1982; MacEwen and Vernot, 1972)

Attachment 11

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

CUMENE
(CAS Reg. No. 98-82-8)



ORNL Staff Scientist: Sylvia Milanez

Chemical Manager: John P. Hinz

Chemical Reviewer: Ursula Gundert-Remy

Chemical Reviewer: Lynn M. Beasley

INTRODUCTION

- Cumene is a colorless liquid with sharp, penetrating, aromatic odor. It is poorly soluble in water (0.005 g/100 mL).

- Cumene is a natural component of petroleum and is present in tobacco smoke. It is a high production volume chemical: in 1995, U.S. production capacity was ~6.4 billion lbs.

- Cumene vapor can be readily absorbed by the respiratory tract. The primary toxic effect of cumene is CHS depression, characterized by changes in motor activity. Sufficiently high exposures lead to narcosis, internal hemorrhage of numerous organs, and death.

- Cumene also causes irritation of the eyes, skin, and mucous membranes at concentrations that cause CNS effects. It is not a very potent irritant (e.g. RD_{50} ~2100 ppm).

INTRODUCTION, cont'd.

- Based on its vapor pressure of 4.6 mm Hg at 25°C, cumene saturated vapor pressure can be calculated as 6100 ppm. Several studies report exposure concentrations >6100 ppm, in which case the actual cumene vapor concentration is unknown, or whether exposure is actually to a mixture of cumene vapor and aerosol.

$$\text{Saturated vapor density} = \frac{\text{Vapor pressure (atm) x MW}}{\text{0.082 l-atm/mol/K x temperature (°K)}}$$

- 9 cumene odor thresholds reported, 0.005-1.3 ppm, in secondary source, which stated that values of 0.008, 0.047, and 0.132 ppm were the most reliable (AIHA 1989)

- Using 0.008 ppm as the POD, a Level of Distinct Odor Awareness (LOA) of 0.017 ppm was calculated for cumene using methodology of van Doorn et al (2002). *I will add this calculation to the TSD.*

- The significance of the calculated LOA is unclear, considering the large spread of reported cumene odor thresholds.

DERIVATION of AEGL VALUES FOR CUMENE

- For all three AEGL levels, effects were based on neurotoxicity (manifestations of CNS depression)

- Time scaling for all three AEGL levels was performed using $C^2 \times t = k$ (ten Berge et al. 1986); n=2 was determined from cumene neurotoxicity data.

- Use of n=2 was supported by the derivation of n=2 for the related compound toluene, based on similar neurotoxic effects. Unlike for toluene, however, blood steady-state cumene levels were not attained during a 6-hour exposure, so values for all time points were scaled using the ten Berge equation.

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
150 ppm	**87 ppm**	**61 ppm**	**31 ppm**	**22 ppm**

NTP 2004. Fischer F344 rats (5/sex/dose) and B6C3F1 mice (5/sex/dose) inhaled 0, 250, 500, 1000, 2000, or 4000 ppm for 6 hrs/day, 5 days/week, for 14 exp.

Effects: RAT

250 ppm: No effects
500 ppm: "Ataxia" on day 1 only (severity undefined)
1000 ppm: Ataxia during all or part of study; inc liver wt; one lung lesion
2000 ppm: Most die on d2-4; all lethargic from d1, dyspnea from d3, ↓BW, testes, thymus wt, ↑ liver wt; lesions: lung, liver, kidney, bladder
4000 ppm: All die after 1 day; lesions in lung, respiratory pleura

Effects: MOUSE

250 ppm: No effects
500 ppm: Inc liver wt
1000 ppm: F died day 3 or 4; all had ataxia or lethargy from day 1; inc liver wt
2000 ppm: All died day 2; all lethargic starting on day 1; inc liver wt
4000 ppm: All died day 1

Endpoint: Subtle reversible neurological effects not detected by standard cageside observation, but at threshold of detectability in the FOB (one 6-hr exposure to 250 ppm).

Total Uncertainty Factor: 10

Interspecies: 3: The AEGL-1 endpoint was very mild and based on data from two species
Intraspecies: 3: CNS depression due to a lipid-soluble narcotic is not expected to vary by more than a factor of 3 in the human population

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
300 ppm	**170 ppm**	**120 ppm**	**61 ppm**	**43 ppm**

Bushy Run 1989. Fischer F344 rats (10/sex/dose) inhaled 0, 100, 500, or 1200 ppm for 6 hours. FOB was performed pre-exposure and 1, 6, and 24 hours post-exposure, after which rats were sacrificed but not necropsied.

Effects:

100 ppm: No toxicity

500 ppm: Mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex)

1200 pm: As 500 ppm; also found increased incidence or severity of gait abnormalities and decreased rectal temperature.

Endpoint: Mild reversible neurological effects that could impede the ability of humans to escape (500 ppm)

Total Uncertainty Factor: 10

Interspecies: 3: The most sensitive species was used and variability among species was not great (similar neurotoxic effects occurred in rats and mice at concentrations within a factor of 2)

Intraspecies: 3: CNS depression due to a lipid-soluble narcotic is not expected to vary by more than a factor of 3 in the human population.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
720 ppm	**420 ppm**	**290 ppm**	**150 ppm**	**100 ppm**

Bushy Run 1989. Fischer F344 rats (10/sex/dose) inhaled 0, 100, 500, or 1200 ppm for 6 hours. FOB was performed pre-exposure and 1, 6, and 24 hours post-exposure, after which rats were sacrificed but not necropsied.

Effects:

100 ppm: No toxicity

500 ppm: Mild reversible neurological changes (increased activity and decreased toe-pinch withdrawal reflex)

1200 pm: As 500 ppm; also found increased incidence or severity of gait abnormalities and decreased rectal temperature.

Endpoint: Threshold for lethality due to CNS depression

Total Uncertainty Factor: 10

Interspecies: 3: The conc. that led to fatal CNS depression varied less 3-fold among species, and a repeat-exposure study indicated that the POD would not exceed the severity of AEGL-3

Intraspecies: 3: CNS depression due to a lipid-soluble narcotic is not expected to vary by more than a factor of 3 in the human population

Summary of AEGL Values for Cumene (ppm)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1[a] (Non-disabling)	150	87	61	31	22	Subclinical or subtle CNS effects in rats (NTP 2004)
AEGL–2 (Disabling)	300	170	120	61	43	Mild neurotoxicity in rats (Bushy Run 1989)
AEGL–3 (Lethal)	720	420	290	150	100	Lethality threshold due to CNS depression in rats (Bushy Run 1989)

Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

An odor detection threshold (OT_{50}, i.e., concentration at which 50% of the odor panel observed an odor without necessarily recognizing it) of 0.008 ppm was obtained for cumene from Hellman and Small (1974). The same citation listed an OT_{50} of 0.30 for n-butanol, as compared to the reference value of 0.04 ppm as the odor threshold provided by van Doorn et al (2002). Based on the differences in n-butanol values from the two sources, an "inter-laboratory" correction factor is applied to cumene as follows:

$\frac{0.04 \text{ ppm n-butanol}}{0.3 \text{ ppm n-butanol}}$ X 0.008 ppm OT_{50} cumene = **0.00107 ppm "corrected" OT_{50} cumene**

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = k_w \times \log (C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of $k_w = 2.33$ will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C / 0.00107) + 0.5$, which can be rearranged to
$\log (C / 0.00107) = (3 - 0.5) / 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 0.00107 = 0.0071$ ppm
$C = 11.8 \times 0.00107 = 0.0126$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33

LOA = C x 1.33 = 0.0126 ppm x 1.33 = 0.017 ppm

The LOA for cumene is 0.017 ppm.

Questions Posed to NTP Study Director for Cumene Inhalation Toxicity Studies (Sept 2004)
From"Chan, Po (NIH/NIEHS)" <chanp@niehs.nih.gov>
Subject: Request for information on CUMENE (98-82-8)
To'Sylvia Milanez' <milanezs@ornl.gov>

Q1. The reporting of "ataxia" for male and female rats at 500 ppm in the 14-day study -- how would this ataxia be characterized? Is it a very severe or a mild lack of coordination? It is unclear why the effect was seen after 1 day but not any later in the 14-day study, and why it was not seen in the 90-day study at all in either species (up to 1000 ppm) ---any idea why?

A1. Ataxia indicates that the rat was moving in an uncharacteristic gait after 6 hours of exposure to cumene. Apparently, the rats recovered during the night and developed tolerance in the second day.

Q2. Lethargy and ataxia are never reported for the same animal on one day - (how) are these mutually exclusive? What are the choices of descriptors for neurological effects besides ataxia and lethargy?

A2. Lethargy was seen after exposure stopped and the rats were not moving even though they were awake. Apparently the rats did not drink and eat and was dehydrated and losing weight. Lethargy was recorded in rats exposed to high concentration whereas ataxia occurred in rats exposed to lower concentration of cumene.

---

3. When exactly did death occur for the 2000 and 4000 ppm rats and mice in the 14-day study?? For example, on the web under the column "days on study", it says "2" for 2000 ppm and "1" for 4000 ppm. So for example, for 4000 ppm, did the animals die during the exposure or the next day before the observation, and for 2000 ppm did the animals actually receive 2 exposures and then die, or did they die some time after the start of the 2nd exposure. (I ask these nit-picky questions because I am trying to project as to what might happen from a single exposure).

A3. The animals were observed (checked) twice daily (in the early morning and late afternoon) for moribundity and mortality. Animals found dead late in the afternoon hours on the first day of exposure was recorded as dead on day 1.

Q4. How were the cumene atmospheres generated and monitored?

A4. Preheated cumene was pumped onto glass beads within a heated glass column. Heated nitrogen flowed through the column and carried the vapor out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump. The vapor was mixed with heated air before it entered a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, generator nitrogen flow rate, and dilution air-flow rate. The exposure operator monitored all three components. The pressure in the distribution manifold was kept fixed to ensure constant flows throught the manifold and into the exposure chamber. The concentration of cumene in the exposure chambers was determined using an on-line, HP-6890 GC, equipped with an FID and a DB-5 capillary column. The relationship between the response of the on-line GC and the concentration of cumene in the exposure chamber was determined by independent analysis of sorbent tube (ORBO-101; graphitized carbon black, Supelco, Bellefonte, PA) samples taken directly from the exposure chambers during exposure periods.

THIRD SET OF (FOLLOW-UP) QUESTIONS

Q5. Was the same observation procedure (twice daily, etc.) used for the 14-day study as for the 90-day study?
A5. Yes

Q6. Were the animals ever observed during exposure? [The NTP site states that observations need to be at least 6 hours apart - does this mean animals were always observed before and after exposure but never during exposure?] Were any notes recorded of observations during exposure (and what were they)?

A6. The exposure chambers have glass front and back doors. During exposure, the technician kept an eye (peeped
through the glass door) on the animals and any abnormality observed was recorded. The animals were not "examined."

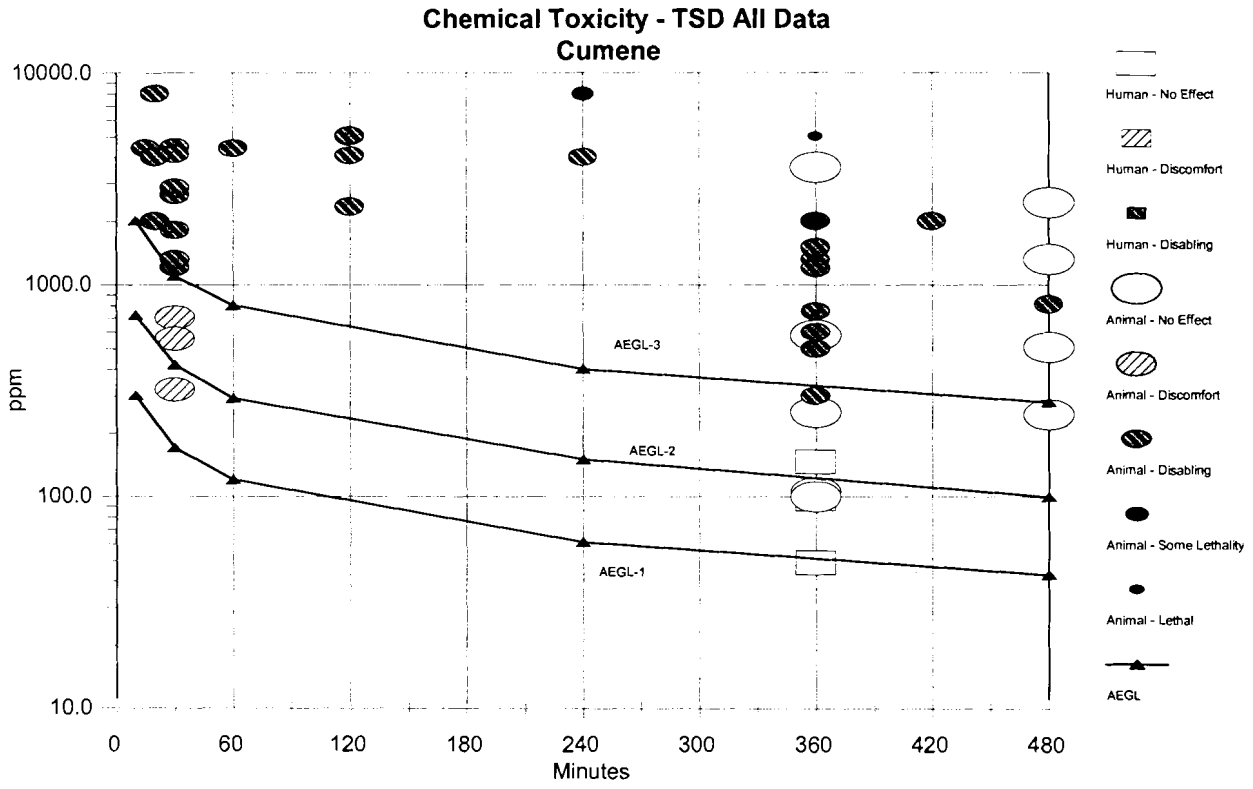
Q7. How soon after the 6-hour exposure ended was the second daily observation made - was this a specified duration or did it vary day-to-day?

A7. Usually at the end of the shift before the technician left for home.

Q8. Are there any plans to conduct FOB (functional observational battery) tests on rats or mice with cumene?

A8. No. FOB tests were reported by Cushman et al., J. Am. College Toxicol. 14129-147, 1995. The tests were considered
adequate.

Category Plot for Cumene



NAC/AEGL Meeting 34: September 21-23, 2004

Attachment 12

Chemical: ETHYLENE OXIDE **CAS Reg. No.:**

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

~~Chemical Manager~~: BILL GULLEDGE PRESENTATION **Staff Scientist:** → Given by Bill Snellings

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.

NR= Not Recommended due to_____

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

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

Bill Snellings (Bill Gulledge) Presentation 9/2004

Attachment 12

Current Proposed AEGL-2 Value

Times	Concentration (ppm)
10 minutes	80
1/2 hour	80
1 hour	45
4 hour	14
8 hour	7.9

Background AEGL-2

- Based on Snellings, Dev. Tox. Inhal. Study
- < fetal body weight
- 6 hour / day for 10 days
- 10 and 30-minute value same since a

  6-hour exposure study was used for deriving value

ACC Response

- Based on information already reviewed and presented in the proposed AEGLs document, a 10-minute value can be established

Background

ACC Previous Response

- Use Saillenfait Dev. Tox. Inhalation Study
- 0.5 and 1.5 hour exposures for 10 days

Dr. Kowetha Davidson's Remarks

Study Unreliable

- 1200 ppm = effects mouse (Generoso)
- no dose response in Saillenfait
- controls were different from each other

1200 ppm Exposure Differences

	Saillenfait	Generoso
Species	rat	mouse
Analytical	GC	IR*
Exposure Actual	1198 ± 95	unknown
Exposure Range	1047 – 1355	unknown
Exposure Duration (hr/d)	0.5	1.5
Exposure Duration (d)	10	4
Maternal Tox.	None	yes (unknown)
Fetal Tox.	> variations (questionnable)	> malformations deaths

*path length for 500 ppm = 9.75m
path lengh for 1200 ppm = 2.75 m

Saillenfait – Dose Response
Fetal body weight (male)

Exposure (ppm • hour / day)	Percent Controls
200	0%
300*	+1%
400	+2%
600	-1%
600*	0%
1200	-6%**
1800	-10%**

* based on mean of two normal controls
** Significant difference

Saillenfait - -Control # 2 Abnormal

	Control 1	Control 2	Control 3
Fetal body weight (males)	**5.75**	**6.39**	**5.79**
Live fetuses/litter	13.3	6.8	14.7
Fetal body wt 300 ppm• hr/ d		**5.72**	
Fetal body wt. 600 ppm• hr/ d		**5.84**	
Fetal body wt. 600 ppm• hr/ d	**5.70**		

Authors Summary

- Exposed animals within historical control
- Attributable to high control fetal weight along with low number of live fetuses
- Reason for abnormal control - - unknown
- Conclusion 300 and 600 ppm are NOELs

Derivation of AEGL-2 Value

Derivation	(Current) Based on Snellings	(Proposed) Based on Saillenfait (1.5h)	(Proposed) Based on Snellings	(Proposed) Based on Saillenfait (0.5h)
$C^n X t = k$				
effect	< fetal wt. 100 ppm	< fetal wt. 800 ppm	< fetal wt. 100 ppm	none (1200 ppm highest)
t	6 hour	1.5 hour	6 hour	0.5 hour
n	1.2	1.2	1.2	1.2
C	100/10 = 10 ppm	800/10 = 80 ppm	100/10 = 10 ppm	1200/10 = 120 ppm
k	95.09359155	288.2698642	95.09359155	156.3102651
10 minutes	80	499	198	>300
1/2 hour	80	200	80	>120
1 hour	45	112	45	>67
4 hour	14	35	14	>21
8 hour	7.9	20	7.9	>12
added safety	10 days of exposure	10 days of exposure	10 days of exposure	10 days of exposure

Summary

- Saillenfait acceptable study
- Exposures at 0.5 hours at 1200 ppm were without effects
- Exposures at 1.5 hours at 800 ppm resulted in < fetal body wt
- Derivations for 10 min AEGL-2 should consider the 0.5 or 1.5 hour Saillenfait data to support a calculated 10 min value

Attachment 13
page 1 of 2

Current main AEGL web page
http://www.epa.gov/oppt/aegl/

The Development of
Acute Exposure Guideline Levels (AEGLs)
A collaborative effort of the public and private sectors worldwide

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.

SOP

The AEGL Standard Operating Procedures section "Purpose and Objectives of the AEGL Program and the NAC/AEGL Committee" (page 21) states:

> "The primary purpose of the AEGL program and the NAC/AEGL Committee is to develop guideline levels for once-in-a-lifetime, short-term exposures to airborne concentrations of acutely toxic, high-priority chemicals."

PROPOSED CHANGES (NAC-34 – Sept. 23, 2004)

NEW DEFINITION FOR AEGL WEBSITE

Acute* Exposure Guideline Levels are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, 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 catastrophic exposures.

national

not more than for up to 8hrs

*Definition = Acute exposures are single, ~~non-repetitive~~ exposures.

Current main AEGL web page
http://www.epa.gov/oppt/aegl/

The Development of
Acute Exposure Guideline Levels (AEGLs)
A collaborative effort of the public and private sectors worldwide

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*Definition = Acute exposures are single, non-repetitive exposures.

Appendix A

NAC/AEGL Meeting 34: September 21-23, 2004

from June, 2004 NETHERLANDS MTG.

Chemical: NAC/AEGL-33 Highlights **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

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

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim				
Glenn Leach				
John Morawetz				
Richard Niemeier				
~~Marinelle Payton~~				
Susan Ripple				
George Rodgers				
Marc Ruijten				
George Rusch, Chair				
Robert Snyder				
Richard Thomas				
George Woodall				
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.

* Minutes approved unanimously.

NR= Not Recommended due to_____

AEGL 1	**Motion by:** Marc Ruijten	**Second by:** Robert Snyder	
AEGL 2	**Motion by:**_____	**Second by:**_____	
AEGL 3	**Motion by:**_____	**Second by:**_____	
LOA	**Motion by:**_____	**Second by:**_____	

Approved by Chair: _____ **DFO:** _____ **Date:** 9/21/04

Appendix B
of NAC-34
highlights

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 $C^n x\ t = k$, 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.

Appendix B
of NAC-34
Highlights

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

APPENDIX C

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: ACETONE CYANOHYDRIN **CAS Reg. No.:** 75-86-5

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

Chemical Manager: ERNIE FALKE **Staff Scientist:** PETER GRIEM

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y				Nancy Kim	Y			
Steven Barbee	Y				Glenn Leach	Y			
Lynn Beasley	N/p (Not present)				John Morawetz	Absent			
Robert Benson	Y				Richard Niemeier	N/p (Not present)			
Jonathan Borak	Y				~~Marinelle Payton~~	———	———	———	
William Bress	Y				Susan Ripple	N/p (Not present)			
George Cushmac	Y				George Rodgers	Y			
Ernest Falke	Y				Marc Ruijten	Y			
~~Alfred Feldt~~	———	———	———		George Rusch, Chair	Y			
John Hinz	Y				Robert Snyder	Absent			
Jim Holler	Y				Richard Thomas	Y			
Tom Hornshaw	Y				George Woodall	Y			
~~Warren Iederberg~~	———	———	———						
					TALLY	17/17			
					PASS/ FAIL	P			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (2.5)	, (2.5)	, (2.0)	, (1.3)	, (1.0)
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.

Motion: Acceptance of COT comments (AEGL-1 values)

NR= Not Recommended due to_____

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

Approved by Chair: [signature] **DFO:** Jennifer A. Camacho **Date:** 9/22/04

NAC/AEGL Meeting 34: September 21-23, 2004 Appendix D

Chemical: TETRANITROMETHANE **CAS Reg. No.:** 509-14-8

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

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y	Y	Y		Nancy Kim	Y	Y	Y	
Steven Barbee	Y	Y	Y		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Y		John Morawetz	Absent	Absent	Absent	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Jonathan Borak	Y	Y	Y		~~Marinelle Payton~~	—	—	—	
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~~	—	—	—		George Rusch, Chair	Y	Y	Y	
John Hinz	Y	Y	Y		Robert Snyder	Absent	Absent	Absent	
Jim Holler	Y	Y	Y		Richard Thomas	Y	Y	Y	
Tom Hornshaw	Y	Y	Y		George Woodall	Y	Y	Y	
~~Warren Iederberg~~	—	—	—						
					TALLY	20/20	20/20	20/20	
					PASS/ FAIL	P	P	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(0.66 ppm)	,(0.66)	,(0.52)	,(0.33)	,(0.17)
AEGL 3	,(2.2)	,(2.2)	,(1.7)	,(1.1)	,(0.55)
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.

One motion to accept 3 sets of values

NR= Not Recommended due to insufficient data

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

Approved by Chair: _____ **DFO:** Jim J. Canales **Date:** 9/22/04

Appendix E

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: PROPYLENE OXIDE **CAS Reg. No.:** 75-56-9

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

Chemical Manager: JIM HOLLER **Staff Scientist:** CLAUDIA TROXEL

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

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	P	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	Absent	Absent	Absent	
Richard Niemeier	Y	Y	Y	
~~Marinelle Payton~~	—	—	—	
Susan Ripple	Y	Y	Y	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	N	Y	
George Rusch, Chair	Y	~~NV~~ Y	Y	
Robert Snyder	P	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Absent	Y	Y	
TALLY	13/13	12/13	18/18	
PASS/ FAIL	P	P	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(73 ppm)	,(73ppm)	,(73 ppm)	,(73ppm)	,(73 ppm)
AEGL 2	,(440 ppm)	,(440 ppm)	,(290 ppm)	,(130 ppm)	,(~~85~~ 86 ppm)
AEGL 3	,(1300 ppm)	,(1300 ppm)	,(~~880~~ 870 ppm)	,(390 ppm)	,(260 ppm)
LOA	21 ppm				
* = ≥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.

LOA approved unanimously by hand-voting

NR= Not Recommended due to_____

AEGL 1 **Motion by:** ~~Bob Benson~~ Ruijten **Second by:** ~~Jim Holler~~ Holler Y:13 A:3
AEGL 2 **Motion by:** Rodgers **Second by:** Thomas Y:12 N:1 A:4
AEGL 3 **Motion by:** Benson **Second by:** Holler Y:18
LOA **Motion by:** **Second by:**

Approved by Chair: [signature] **DFO** Lynn A. Conaclo **Date:** 9/22/04

APPENDIX F

Chemical: ACETALDEHYDE **CAS Reg. No.:** 75-07-0

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

Chemical Manager: MARIELLE PAYTON **Staff Scientist:** JOHN SCHEFFLER

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	N	N (Y)	Y	
Steven Barbee	Y	N (Y)	Y	
Lynn Beasley	Y	N (Y)	Y	
Robert Benson	Y	Y (N)	Y	
Jonathan Borak	Y	N (Y)	P	
William Bress	Y	N (Y)	Y	
George Cushmac	Y	N (Y)	Y	
Ernest Falke	Y	N (Y)	Y	
~~Alfred Feldt~~	~~Absent~~	—	—	
John Hinz	Y	N (Y)	Y	
Jim Holler	Y	N (Y)	Y	
Tom Hornshaw	P	N (Y)	Y	
~~Warren Iederberg~~	—	—	—	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	N	N (Y)	Y	
Glenn Leach	Y	N (Y)	Y	
John Morawetz	N	N (Y)	P	
Richard Niemeier	Y	N (Y)	Y	
~~Marielle Payton~~	—	—	—	
Susan Ripple	Y	N (Y)	Y	
George Rodgers	Y	N (Y)	Y	
Marc Ruijten	Y	Y (N)	Y	
George Rusch, Chair	Y	N (Y)	Y	
Robert Snyder	N	N (Y)	Y	
Richard Thomas	Y	N (Y)	Y	
George Woodall	Y	N (Y)	Y	
TALLY	~~17~~ 18	~~2~~ 22 (~~20~~ 22)	~~20~~ 20	
PASS/ FAIL	P	F (P)	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	45 ppm ,( )	45 ppm ,( )	45 ppm ,( )	45 ppm ,( )	45 ppm ,( )
AEGL 2	~~1100~~ ~~(340)~~ ppm ,(340)	~~1100~~ (340) ppm ,( )	~~710~~ (240) ppm ,( )	~~570~~ (170) ppm ,( )	~~380~~ (110) ppm ,( )
AEGL 3	1100 ppm ,( )	1100 ppm ,( )	840 ppm ,( )	530 ppm ,( )	260 ppm ,( )
LOA	0.56 ppm				
* = ≥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.

LOA motion was carried unanimously by hand-voting.

NR= Not Recommended due to _____

AEGL 1 Motion by: Benson **Second by:** Hinz
AEGL 2 Motion by: Ruijten → (Woodall) **Second by:** Benson → (Thomas)
AEGL 3 Motion by: ~~Niemeier~~ Alexeeff **Second by:** ~~Thomas~~ Hinz
LOA Motion by: Benson **Second by:** ~~Hinz~~ Hinz

Approved by Chair: _____ **DFO:** Iris A. Camacho **Date:** 9/2/04

Appendix G

NAC/AEGL Meeting 54: September 21-23, 2004

Chemical: VINYL ACETATE **CAS Reg. No.:** 108-05-4

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

Chemical Manager: RICHARD THOMAS **Staff Scientist:** CLAUDIA TROXEL

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y	N	P		Nancy Kim	Y	N	Y	
Steven Barbee	Y	Y	Y		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Absent		John Morawetz	P	P	Absent	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Jonathan Borak	P	P	P		~~Marinelle Payton~~	—	—	—	
William Bress	Y	Y	Y		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rodgers	Y	P	Y	
Ernest Falke	Y	P	P		Marc Ruijten	Y	Y	Y	
~~Alfred Feldt~~	—	—	—		George Rusch, Chair	Y	Y	Y	
John Hinz	Y	Y	Y		Robert Snyder	Y	P	P	
Jim Holler	Y	Y	Y		Richard Thomas	Y	Y	Y	
Tom Hornshaw	Y	N	P		George Woodall	Y	P	Y	
~~Warren Jederberg~~	—	—	—						
					TALLY	Y 20 A 20	Y 13 16	Y 15 15	
					PASS/ FAIL	P	P		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	6.7 ppm ,( )	6.7 ppm ,( )	6.7 ppm ,( )	6.7 ppm ,( )	6.7 ppm ,( )
AEGL 2	230 ppm ,( )	230 ppm ,( )	180 ppm ,( )	110 ppm ,( )	75 ppm ,( )
AEGL 3	760 ppm ,( )	760 ppm ,( )	610 ppm ,( )	380 ppm ,( )	250 ppm ,( )
LOA	0.25 ppm				
* = ≥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.

AEGL 2 values are contingent to histopathology report.
*LOA motion carried unanimously by hand-voting.

NR= Not Recommended due to_____

AEGL 1 Motion by: Ruijten **Second by:** Alexeeff
AEGL 2 Motion by: Ruijten **Second by:** Hinz
AEGL 3 Motion by: Benson **Second by:** Ruijten
LOA Motion by: John Hinz **Second by:** Bress

Approved by Chair: [signature] **DFO:** Jack Ceraldo **Date:** 9/21/04

Appendix H

NAC/AEGL Meeting 54: September 21-23, 2004

Chemical: DISULFUR DICHLORIDE **CAS Reg. No.:** 10025-67-9

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

Chemical Manager: ERNIE FALKE **Staff Scientist:** KOMETHA DAVIDSON

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y	P	Y		Nancy Kim	Y	Y	Y	
Steven Barbee	Y	Y	Y		Glenn Leach	Y	Y	Y	
Lynn Beasley	Y	Y	Y		John Morawetz	Absent	Absent	Absent	
Robert Benson	Y	P	Y		Richard Niemeier	Y[a]	Y	Y	
~~Jonathan Borak~~	~~Absent~~	P	P		~~Marmelle Payton~~	—	—	—	
William Bress	Y	Y	Y		Susan Ripple	Y[a]	Y	Y	
George Cushmac	Y	Y	Y		George Rodgers	Y	N	Y	
Ernest Falke	Y	Y	Y		Marc Ruijten	Y	Y	Y	
~~Alfred Feldt~~	—	—	—		George Rusch, Chair	Y	Y	Y	
John Hinz	P	Y	Y		Robert Snyder	Absent	Absent	Absent	
Jim Holler	Y	Y	Y		Richard Thomas	Y	Y	Y	
Tom Hornshaw	Y	Y	Y		George Woodall	P	Y	Y	
~~Warren Jederberg~~	—	—	—						
					TALLY	17/17	16/17	19/19	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.67ppm ,( )	0.67 ,( )	0.53 ,( )	0.33 ,( )	0.17 ,( )
AEGL 2	8.1 ,( )	8.1 ,( )	6.4 ,( )	4.0 ,( )	2.0 ,( )
AEGL 3	,(19)	,(19)	,(15)	,(9.6)	,(4.8)
LOA	NO LOA				
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

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

NR= Not Recommended due to_____

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/22/04

Appendix I

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: DIBROMOETHANE **CAS Reg. No.:** 106-93-4

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

Chemical Manager: NANCY KIM **Staff Scientist:** KOWETHA DAVIDSON

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

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,(96ppm)	,(40)	,(26ppm)	,(13ppm)	,(10ppm)
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.

Note: AEGL-1 and AEGL-2 values were not developed.

NR= Not Recommended due to_____

AEGL 1 **Motion by:**_____ **Second by:**_____
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:** Richard Thomas **Second by:** George Woodall
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: [signature] **DFO** [signature] **Date:** 9/22/04

Appendix J

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: HYDROXYLAMINE **CAS Reg. No.:** 7803-49-8

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

Chemical Manager: GEORGE CUSHMAC **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexceff					Nancy Kim				
Steven Barbee	Absent				Glenn Leach				
Lynn Beasley					John Morawetz	Absent			
Robert Benson					Richard Niemeier				
Jonathan Borak					~~Marinelle Payton~~	—			
William Bress					Susan Ripple				
George Cushmac					George Rodgers				
Ernest Falke	Absent				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/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 3	,(NR)	,(NR)	,(NR)	,(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.

AEGL values were not derived due to absence of data
+ Motion approved unanimously

NR= Not Recommended due to_____

AEGL 1 Motion by: G Rogers **Second by:** Thomas
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/22/04

Appendix K

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: CUMENE **CAS Reg. No.:** 98-82-8

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

Chemical Manager: JOHN HINZ **Staff Scientist:** SYLVIA MILANEZ

NAC Member	AEGL1	AEGL2	AEGL3	LOA
George Alexeeff	Y (Y)	N	P	
Steven Barbee	N (Y)	P	Y	
Lynn Beasley	N (Y)	Y	Y	
Robert Benson	Y (Y)	Y	Y	
Jonathan Borak x	Absent	Absent	Absent	
William Bress	N (Y)	Y	Y	
George Cushmac	N (Y)	Y	Y	
Ernest Falke	N (Y)	Y	Y	
~~Alfred Feldt~~	—	—	—	
John Hinz	N (Y)	Y	Y	
Jim Holler x	Absent	Absent	Absent	
Tom Hornshaw	N (Y)	Y	Y	
~~Warren Iederberg~~	—	—	—	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y (P)	Y	Y	
Glenn Leach	Y (Y)	Y	Y	
John Morawetz x	Absent	Absent	Absent	
Richard Niemeier	N (Y)	Y	Y	
~~Marinelle Payton~~	—	—	—	
Susan Ripple	N (Y)	Absent	Y	
George Rodgers	Y (Y)	Y	Y	
Marc Ruijten	N (Y)	Y	Y	
George Rusch, Chair	P (Y)	Y	Y	
Robert Snyder	Y (Y)	Y	Y	
Richard Thomas x	Absent	Absent	Absent	
George Woodall	N (Y)	Y	Y	
TALLY	5/17 (17/17)	15/16	17/17	
PASS/ FAIL	F (P)	P	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (50 ppm)	, (50 ppm)	, (50 ppm)	, (50 ppm)	, (50 ppm)
AEGL 2	, (550 ppm)	, (380 ppm)	, (300 ppm)	, (190 ppm)	, (130 ppm)
AEGL 3	, (1300 ppm)	, (920 ppm)	, (730 ppm)	, (460 ppm)	, (300 ppm)
LOA	0.017 ppm				
* = ≥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.

LOA motion was carried unanimously by hand-voting

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Benson / (Benson) **Second by:** Kim / (George Rodgers)
AEGL 2 **Motion by:** Ruijten **Second by:** Hinz
AEGL 3 **Motion by:** Ruijten **Second by:** Benson
LOA **Motion by:** Bress **Second by:** Ripple

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/23/04

Appendix L

NAC/AEGL Meeting 34: September 21-23, 2004

Chemical: AEGL Definition **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

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

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

PPM, (mg/m³)	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: Falke **Second by:** George Rodgers.
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/23/04