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

December 13-15, 2004

Final Meeting-35 Highlights

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

INTRODUCTION

Chairman George Rusch welcomed the committee and thanked Surender Ahir for the meeting arrangements.

The draft NAC/AEGL-34 meeting highlights were reviewed. One editorial correction was suggested and has been incorporated into the highlights. A motion was made by Richard Thomas and seconded by Warren Jederburg to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by a show of hands. The final version of the NAC/AEGL-34 meeting highlights is attached (Appendix A).

The highlights of the NAC/AEGL-35 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-35 Agenda.

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

Comments from the *Federal Register Notice* of September 7, 2004, on the proposed AEGL values for acrolein, chloroform, epichlorohydrin, n,n-dimethylformamide, nitrogen dioxide, peracetic acid, and trichloroethylene were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

Acrolein (CAS No. 107-02-8)

Chemical Manager: Robert Snyder, Rutgers University
Staff Scientist: Cheryl Bast, ORNL

Comments from the *Federal Register Notice* on the proposed AEGL values for acrolein were reviewed and discussed by Cheryl Bast (Attachment 3). Comments were received from George Alexeeff (California EPA) and Robert Sills (Michigan Department of Environmental Quality). Dr. Alexeeff commented that descriptions of points-of-departure for AEGL-1 and AEGL-2 needed clarification with regard to NOAEL vs. LOAEL. Cheryl Bast provided alternate text to clarify the justifications for point-of-departure selection. Dr. Sills comments were focused on AEGL-1. He questioned holding AEGL-1 values constant across all time points and the use of an intraspecies UF of 3. These concerns were addressed by referencing appropriate section of the SOP. Dr. Sills also commented on the selection of the key study for AEGL-1 derivation (Weber-Tschopp et al., 1977) and suggested an alternative study (Darley et al., 1960) that was not included in the TSD. Cheryl Bast explained that the Weber-Tschopp study was more robust and utilized better methodology and analytical techniques than the Darley study. A summary of the Darley study will be included in the revised TSD for completeness. There was agreement to remove the use of occupational guidelines in the rationale for AEGL-2 values. Following this discussion, a motion was made by Robert Snyder and seconded by Marc Ruijten to raise the acrolein values to interim. The motion passed unanimously by a show of hands (Appendix B).

Chloroform (CAS No. 67-66-3)

Chemical Manager: Steven Barbee, Arch Chemicals
Staff Scientist: Robert Young, ORNL

Comments from the *Federal Register Notice* on the proposed AEGL values for chloroform (Attachment 4) were reviewed and discussed by Bob Young. Comments were received from George Alexeeff (California EPA), who requested clarification regarding the use of a LOAEL for fetotoxicity and embryolethality rather than a NOAEL (i.e., gestational exposure of rats to 100 ppm vs 30 ppm). Bob Young provided justification for retaining current AEGL values by noting that the use of 30 ppm would result in AEGL-2 values (40, 27, 21, 13, and 9.7 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hrs, respectively) that are inconsistent with available data. Specifically, multiple exposure (i.e., years) to chloroform at exposure concentrations of 6.2 - 237 ppm resulted in nausea, flatulence, thirst, increased micturition and urinary discomfort, and behavioral effects (Challen et al., 1958) which are not of AEGL-2 severity. It was noted that some studies indicate chloroform to be a developmental toxicant in rats following multiple inhalation exposures to 100 or 300 ppm during gestation but these effects often involved decreased feed consumption and decreased maternal body weight. Although the AEGL-2 values were developed based upon effects occurring following multiple (8-10 day) exposures to 100 ppm (i.e., a LOAEL), it was assumed that these effects resulted from a single exposure. For this reason and the equivocality of chloroform developmental toxicity, this was considered a conservative estimate of the point-of-departure (POD) for AEGL-2 development. Marc Ruijten suggested that a report by RIVM (van

raaij, Janssen, and Piersma, 2003) be attached to the meeting summary due to its relevance regarding developmental toxicity as a POD for AEGLs (Attachment 5). Following this discussion, a motion was made by Robert Benson and seconded by Marc Ruijten to raise the chloroform values to interim. The motion passed by a show of hands (Appendix C).

N,N-Dimethylformamide (DMF) (CAS No. 68-12-2)

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

Comments from the *Federal Register Notice* on the proposed AEGL values for n,n-dimethylformamide were reviewed and discussed by Claudia Troxel (Attachment 6). Comments were received from E.I. duPont Nemours, Inc. (a producer of DMF), who stated that overall the AEGL values are too conservative and do not agree with the body of data on DMF. Specifically, the 4-hour AEGL-2 of 55 ppm is inconsistent with the observation that individuals were exposed to 87 ppm DMF for 4 hours in a metabolism study. The 10-minute AEGL-3 of 320 ppm is inconsistent with the fact that no deaths occurred in monkeys exposed to 500 ppm DMF or rats exposed to 800 ppm for 13-weeks. The NAC did agree that AEGL values for DMF are conservative, and there is a statement to that effect in the AEGL-3 derivation section. However, because there are no viable alternatives for derivation of AEGL values for DMF, a motion was made by Tom Hornshaw and seconded by Nancy Kim to raise the DMF values to interim. The motion passed by a show of hands (Appendix D). A letter will be sent to duPont explaining that FR comments were acknowledged.

Epichlorohydrin (CAS No. 106-89-8)

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

Comments from the *Federal Register Notice* on the proposed AEGL values for epichlorohydrin were reviewed and discussed by Richard Thomas (Attachment 7). Comments were received from Ernest Falke who commented that the odor threshold should not be used as support for AEGL-1 and that secondary sources should not be used for derivation of AEGL values. Richard Thomas, George Woodall, and Tom Hornshaw also agreed that the AEGL-1 values needed revision because the NAC no longer bases AEGL-1 values on odor detection. Two options were presented. Proposal No. 1 was to use the UCC (1983) report showing pharyngeal irritation in one of four subjects exposed to 68 ppm epichlorohydrin for 2 minutes. Exposure to 136 ppm resulted on ocular and pharengeal irritation in two of the four subjects. Application of an intraspecies UF of 3 to the POD of 68 ppm and time scaling using n= 0.87, would result in a 10-min AEGL-1 value of 3.6 ppm. This value would be adopted for all time points (mild irritation). Proposal No. 2 was to not recommend AEGL-1 values. Additionally, an LOA of 46 ppm was calculated and proposed.

There was then discussion concerning the use of a modifying factor for Proposal No. 1. George Rusch and Thomas Hornshaw suggested applying a modifying factor of 2 or 3. A motion was then made by Thomas Hornshaw and seconded by Susan Ripple to use the UCC study, using 68 ppm as the POD concentration, an intraspecies UF of 3 and a MF of 3. The modifying factor would be applied to the 10-min, 30-min and 1-hr time points due to the weakness of the database, but not to 4- and 8-hrs time points. Marc Ruijten was not comfortable in using a 2-min exposure to derive longer time periods. Peter Bos also indicated that 2-min is not enough time to reach a steady state. The motion was withdrawn. Ernest Falke then noted that were inconsistencies in chamber size suggesting study needs more consideration if it will be finally used in the derivation.

After this considerable discussion, a decision was made to table this chemical until a future meeting in order to re-evaluate all clinical studies (with regard to potential AEGL-1 derivation). Marc Ruijten recommended recalculating the LOA, because the current LOA was not calculated according to the guidelines.

Nitrogen Dioxide (CAS No. 10102-44-0)
Nitric Oxide (CAS No. 10102-43-9)

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

Comments from the *Federal Register Notice* on the proposed AEGL values for nitrogen dioxide/nitric oxide were reviewed and discussed by George Woodall (Attachment 8). One comment was received from George Alexeeff (California EPA), who requested that the NAC reconsider AEGL-1 values because effects were described at the concentration used as the POD for AEGL-1 values. The AEGL-1 values were based on an exposure of exercising asthmatics to 0.5 ppm for 2 hours. Although subjective symptoms were noted in seven of thriteen asthmatics, there were no effects on pulmonary function. John Morawetz then stated that the irritation noted in these studies (Kerr; 1978, 1979) is above the definition of AEGL-1. However, Bob Benson noted that the irritation was mild and was observed in a sensitive subpopulation. The NAC considered the POD a NOAEL for pulmonary function effects in a sensitive subpopulation. Following the discussion, a motion was made by Robert Benson and seconded by George Woodall to raise the nitrogen dioxide/nitric oxide values to interim. The motion passed by a show of hands (Appendix E).

Peracetic Acid (CAS No. 79-21-0)

Chemical Manager: Bill Bress, Vermont
Staff Scientist: Kowetha Davidson, ORNL

Comments from the *Federal Register Notice* on the proposed AEGL values for peracetic acid were reviewed and discussed by Marquea King (Attachment 9). Comments were received from

John Morawetz (International Chemical Workers Union Council) and Thurman Wenzl (Adjunct Associate Professor, University of Cincinnati). Mr. Morawetz recommended that the AEGL-2 values be lowered by time scaling for all values greater than 10 minutes. He was also concerned about the clarity of human exposure time data descriptions. Dr. King explained that time scaling would yield AEGL-2 values approaching AEGL-1 values at longer time points and that the current AEGL-1 values are below any concentration shown to cause irritation in humans. Dr. King and Mr. Morawetz will review the text and primary article's exposure level and time period and adjust the TSD description if necessary. Dr. Wenzl requested clarification on the use of Frazier and Thorbison (1986) data, specifically conversion of ppm hydrogen peroxide to mg/m^3 peracetic acid and the selection of the point-of-departure for AEGL-2, in light of the fact that effects may have been noted at 2 ppm. Dr. King explained that the rationale for converting ppm as hydrogen peroxide to mg/m^3 of peracetic acid is that one mole hydrogen peroxide is equivalent to one mole peracetic acid. The uncertainty regarding effects at 2 ppm was taken into account by using a lower concentration, 1.5 ppm, as the POD for AEGL-2. Following the discussion, a motion was made by Robert Benson and seconded by Marc Ruijten to raise the peracetic acid values to interim. The motion passed unanimously by a show of hands (Appendix F).

Trichloroethylene (CAS No. 79-01-6)

Chemical Manager: Bill Bress, Vermont
Staff Scientist: Peter Bos, RIVM

Comments from the *Federal Register Notice* on the proposed AEGL values for trichloroethylene were reviewed and discussed by Steve Barbee (Attachment 10). Comments were received from John Morawetz (International Chemical Workers Union Council). Mr. Morawetz was concerned that the 10-minute (10,000 ppm) and 30-minute (6100 ppm) AEGL-3 values were too high because they were too close to the narcosis threshold and concentrations where cardiac arrhythmia was noted. Mr. Morawetz suggested adopting the 1-hour AEGL-3 value of 3800 ppm as the AEGL-3 values for 10- and 30-minutes. After discussion, a motion was made by Marc Ruijten and seconded by Bob Benson to adopt the 30-minute AEGL-3 value of 6100 ppm as the 10-minute AEGL-3 value and to add an LOA derivation to the TSD. This approach yielded values in the range of concentrations where anesthesia may be induced, but below concentrations causing cardiac irregularities. The motion carried (YES:18; NO: 0; ABSTAIN: 3) (Appendix. G). A motion was then made by George Rodgers and seconded by Susan Ripple to raise the trichloroethylene values to interim. The motion passed by a by a show of hands (Appendix G).

ADMINISTRATIVE ITEM REGARDING TSDs REVISED AFTER DELIBERATION OF *FEDERAL REGISTER* COMMENTS

Marc Ruijten suggested providing revised TSDs to committee members as well as posting the TSDs on the AEGL website.

ADMINISTRATIVE ITEM REGARDING *FEDERAL REGISTER* COMMENTS FROM NAC MEMBERS

Paul Tobin reported that the EPA FACA office cannot continue to accept comments from FACA members. The committee members are part of the NAC consensus process and provide comments during deliberations, and thus are not part of the public comment process. John Morawetz requested this EPA FACA policy in writing. Paul Tobin will check with FACA management to determine how to handle dissenting opinions.

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 one interim chemical was discussed. Perchloromethyl mercaptan was reviewed by the COT/AEGL Subcommittee at its February 6-8, 2002, meeting.

Perchloromethyl mercaptan (CAS No. 594-42-3)

Staff Scientist: Claudia M. Troxel, CMTox, Inc.
Chemical Manager: Susan Ripple, Dow Chemical

Claudia Troxel discussed the limited data set and COT/AEGL's comments (Attachment 11). The COT/AEGL had three main areas of concern (1) consideration of a MF to account for poor data quality; (2) the AEGL-1 and AEGL-2 values were based on the systemic endpoint of pulmonary infection following a single exposure to an irritant; and (3) the application of an adjusted composite uncertainty factor, rather than individual component UFs. After discussion, a motion was made by Marc Ruijten and seconded by Steve Barbee to base AEGL-3 values on the no-effect-level for death in rats exposed to 9 ppm for 1 hour (Stauffer, 1971); uncertainty factors of 3 each were applied for inter- and intraspecies variability, and time scaling was accomplished using the default values for the exponent 'n' of 1 or 3. The motion also included deriving AEGL-2 values by division of the AEGL-3 values by 3, and adopting AEGL-1 values of 0.013 ppm for all time points. AEGL-1 values are based on mild nasal epithelial changes in rats exposed to 0.13 ppm, 6 hours/day, 5 days/week for 2 weeks (Knapp et al., 1987). An interspecies uncertainty factor of 3 was proposed because minor irritation is not expected to vary greatly between species. An intraspecies uncertainty factor of 3 was also applied because of the steep concentration-response relationship. No MF was applied because of the minor epithelial changes in a repeated exposure study. The calculated LOA of 0.016 ppm will also be included in the TSD. The motion carried (YES:16; NO: 1; ABSTAIN: 1) (Appendix H).

Summary of Interim AEGL Values for Perchloromethyl mercaptan						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	0.013 ppm	Epithelial change in rats (Knapp et al., 1987)
AEGL–2	0.53 ppm	0.37 ppm	0.30 ppm	0.077 ppm	0.037 ppm	⅓ the AEGL-3 values
AEGL–3	1.6 ppm	1.1 ppm	0.90 ppm	0.23 ppm	0.11 ppm	NOEL for death in rats (Stauffer, 1971)
LOA	0.016 ppm					

REVIEW of PRIORITY CHEMICALS

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

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

Bob Benson gave a brief summary of NAC deliberations on this chemical. AEGL values were first discussed in September, 2002. There were a number of questions about PBPK model used to calculate AEGL values. Dr. Bos and colleagues at RIVM provided a revised TSD at the June, 2004 meeting with a detailed explanation of the model. The NAC unanimously endorsed the general approach. Dr. Bos then presented the AEGL values derived from the model. These provisional values were accepted by the NAC. For details of the PBPK approach, the derived AEGL values, and voting, see the minutes of NAC 33 (June 14-16, 2004). At NAC-34 (September 21-23, 2004), it was announced that any NAC members with additional questions submit them to Dr. Bos so any recalculating could be done prior to the December meeting. No comments were received that would alter the values.

Dr. Bos then presented a brief review of the modeling approach and the AEGL values adopted at the June, 2004 meeting (Attachment 12). After a brief discussion, a motion was made by Marc Ruijten and seconded by Susan Ripple to validate the draft provisional values. The motion carried (YES: 20; NO: 0; ABSTAIN: 1) (APPENDIX I).

Summary of AEGL Values for Methylene chloride					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL–1	290 ppm	230 ppm	200 ppm	NR	NR
AEGL–2	1700 ppm	1200 ppm	560 ppm	100 ppm	60 ppm
AEGL–3	12,100 ppm	8500 ppm	6900 ppm	4900 ppm	2100 ppm

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

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

Richard Thomas provided a brief update on the key study used for derivation of AEGL-2 values. The AEGL-2 was based on a study in which exposure for 6 hours to 1000 ppm vinyl acetate caused nasal lesions in rats (Bogdanffy et al., 1987). At NAC-34, AEGL-2 values were approved with the stipulation that the study pathologist be contacted in order to confirm that the lesions were reversible. A report from the pathologist does confirm that the lesions were reversible. Therefore, no additional action is required.

Chloroacetylaldehyde (CAS No. 107-20-0)

Staff Scientist: Peter Bos, RIVM
Chemical Manager: Marinelle Payton, Jackson State University

Peter Bos reviewed the available data for chloroacetylaldehyde (Attachment14). Proposed AEGL-1 (4.9 ppm, 2.0 ppm, 1.1 ppm, 0.35 ppm, and 0.19 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) values were set equivalent to 50% of the AEGL-2 values. This approach was deemed appropriate due to the steep concentration-response curve for chloroacetylaldehyde. Proposed AEGL-2 values were based on lung edema in rats two weeks after a 1-hour exposure to 44 ppm. Uncertainty factors of 3 each were applied for inter- and intraspecies differences, and were considered sufficient because chloroacetylaldehyde is a highly reactive irritant and exhibits a steep concentration-response curve (total UF = 10). A modifying factor of 2 was also applied because the point of departure was a LOAEL rather than a NOAEL. Time scaling was accomplished using $C^n \times t = k$, where the exponent, n = 1.2 (derived from rat lethality data and deemed appropriate because effects at different AEGL levels are if differing severity, but a similar mechanism). Proposed AEGL-3 values were based on a $BMCL_{05}$ of 99 ppm from a 1-hour exposure to rats. Uncertainty factors of 3 each were applied for inter- and intraspecies differences, and were considered sufficient because chloroacetylaldehyde is a highly reactive irritant and exhibits a steep concentration-response curve (total UF = 10). Time scaling was

accomplished using $C^n \times t = k$, where the exponent, n = 1.2, was derived from rat lethality data. Data were insufficient for calculation of an LOA.

After discussion, a motion was made by Bob Snyder and seconded by Bob Benson to adopt AEGL-3 values as proposed. The motion passed (YES: 21; NO: 0; ABSTAIN: 0) (Appendix J).

A motion was then made by Marc Ruijten and Seconded by Warren Jederburg to adopt AEGL-2 values as proposed. The motion passed (YES: 20; NO: 1; ABSTAIN: 0) (Appendix J).

A motion was made by Marc Ruijten and Seconded by Warren Jederburg to base AEGL-1 values on eye and nasal irritation in rats exposed to 5 ppm for 7 hours (Dow, 1952). Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation and a MF of 2 was also applied for LOAEL to NOAEL extrapolation. Time scaling was accomplished using $C^n \times t = k$, where the exponent, n = 1.2. The motion passed (YES: 21; NO: 0; ABSTAIN: 0) (Appendix J).

Summary of AEGL Values for Chloroacetylaldehyde						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	2.3 ppm	2.3 ppm	1.3 ppm	0.40 ppm	0.23 ppm	Ocular and nasal irritation in rats (Dow, 1952)
AEGL–2	9.8 ppm	3.9 ppm	2.2 ppm	0.69 ppm	0.39 ppm	Lung edema in rats (TNO, 1987)
AEGL–3	44 ppm	18 ppm	9.9 ppm	3.1 ppm	1.8 ppm	$BMCL_{05}$ - rat (TNO, 1987)

Propionaldehyde (CAS No. 123-38-6)

Staff Scientist: Peter Bos, RIVM
Chemical Manager: Marinelle Payton, Jackson State University

Peter Bos reviewed the available data for propionaldehyde (Attachment15). Proposed AEGL-1 values were based on mild irritation of the mucosal surfaces in 12 humans exposed to 134 ppm for 30 minutes. This point-of-departure was considered a sub AEGL-1 effect. An intraspecies uncertainty factor of 3 was applied and was considered sufficient because no large differences in kinetics and dynamics are expected for the minor local irritation from propionaldehyde. AEGL-1 values were held constant across time. Proposed AEGL-2 values were based on no effects on nasal epithelium in rats after a 6 hour exposure to 1453 ppm. Inter- and intraspecies uncertainty factors of 3 each were applied and are considered sufficient because larger UFs would conflict with human data and would be inconsistent with acetaldehyde AEGL values (acetylaldehyde has toxicity profile similar to propionaldehyde). Time scaling was accomplished using $C^n \times t = k$, where the exponent, n, was the default value of 3 when extrapolating from longer to shorter time

points and 1 when extrapolating from shorter to longer time points. There were insufficient chemical-specific data for derivation of AEGL-3 values for propionaldehyde. However, propionaldehyde and acetylaldehyde have similar toxicity profiles, and a robust data set exists for acetylaldehyde. Therefore, it was proposed that the AEGL-3 values for acetylaldehyde be adopted as the AEGL-3 values for propionaldehyde. An LOA of 0.64 ppm was calculated.

After discussion, a motion was made by Marc Ruijten and seconded by Richard Niemier to adopt the AEGL-3 values as proposed. The motion passed (YES: 20; NO: 1; ABSTAIN: 0) (Appendix K). A motion was then made by Ernie Falke and seconded by Richard Niemier to adopt the AEGL-2 values as proposed. This motion passed (YES: 21; NO: 0; ABSTAIN: 0) (Appendix K). Then, a motion was made by Ernie Falke and seconded by Richard Thomas to adopt AEGL-1 values as proposed. The motion passed (YES: 21; NO: 0; ABSTAIN: 0) (Appendix K). Finally, a motion was made by Richard Thomas and seconded by Marc Ruijten to adopt the LOA as proposed. This motion passed unanimously by a show of hands.

Summary of AEGL Values for Propionaldehyde						
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	Minor mucosal irritation in humans (Sim and Pattle, 1957)
AEGL–2	330 ppm	330 ppm	260 ppm	170 ppm	110 ppm	NOEL for nasal epithelial effect in rats (Driscoll, 1993)
AEGL–3	1100 ppm	1100 ppm	840 ppm	530 ppm	260 ppm	Acetaldehyde AEGL-3 values adopted ($BMCL_{05;}$ Appleman et al., 1982)
LOA	0.64 ppm					

Biphenyl (CAS No. 92-52-4)

Staff Scientist: Dana Glass, ORNL
Chemical Manager: Richard Thomas, INTERCET

Dana Glass discussed the available human and animal data (Attachment 16). AEGL-1 values were not recommended because of insufficient data. Proposed AEGL-2 values were a three-fold reduction of the AEGL-3 values (2.9 ppm, 2.9 ppm, 2.3 ppm, 1.4 ppm, and 0.73 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively), and were considered an estimated threshold for impaired ability to escape. Proposed AEGL-3 values were based on hyperactivity, basal discharge, rapid respiration, and slight lung congestion in mice exposed to 43 ppm for 4-hour (Cannon Laboratories, Inc., 1977). The point of departure was the highest concentration employed in acute inhalation studies resulting in clinical signs and no treatment-related

mortality. An interspecies incertainty factor of 3 was proposed because clinical signs were similar in different species. An intraspecies uncertainty factor of 3 was also proposed because applying an intraspecies UF of 10 created levels unrealistically low compared to occupational levels. Time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 when extrapolating from longer to shorter time points and 1 when extrapolating from shorter to longer time points. Proposed AEGL-3 values were 8.6 ppm, 8.6 ppm, 6.8 ppm, 4.3 ppm, and 2.2 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. An LOA was not proposed due to insufficient data.

Marc Ruijten asked why biphenyl was on the chemical priority list. Paul Tobin explained that biphenyl is included in the EPA's most hazardous chemical list.

After discussion, a motion was made by Marc Ruijten and seconded by Bob Benson to adopt AEGL-2 values based on a NOEL in mice exposed to 50 ppm 7 hours/day for 13 weeks (the point of departure was 50 ppm for 7 hours). Inter- and intraspecies uncertainty factors of 3 each were applied and were considered sufficient because the AEGL-2 values were based on a NOEL from a subchronic study. Time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 when extrapolating from longer to shorter time points and 1 when extrapolating from shorter to longer time points. The 30-min value was adopted as the 10-min value. The motion passed (YES: 20; NO: 2; ABSTAIN: 0) (Appendix L).

A motion was then made by Warren Jederburg and seconded by Tom Hornshaw not to recommend AEGL-3 values because of a lack of lethality data. The motion passed (YES: 19; NO: 1; ABSTAIN: 2) (Appendix L). Finally, a motion was made by George Woodall and seconded by Nancy Kim not to recommend AEGL-1 values because of insufficient data. This motion passed unanimously by a show of hands.

Summary of AEGL Values for Biphenyl

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Insufficient data
AEGL–2	12 ppm	12 ppm	9.6 ppm	6.0 ppm	4.4 ppm	NOEL in subchronic mouse study (Cannon Laboratories, Inc., 1977)
AEGL–3	NR	NR	NR	NR	NR	Insufficient data

* NR: AEGL-1and AEGL-3 values are not recommended

Butadiene (CAS No. 106-99-0)

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

Peter Bos discussed the available human and animal data (Attachment 17). Proposed AEGL-1 values were based on slight ocular irritation in two human males exposed to 2000 ppm for 7 hours. An intraspecies uncertainty factor of 3 was proposed because no large differences in kinetics or dynamics are expected for the local effects of butadiene. Values were held constant across time because mild irritation is not expected to increase with increased exposure duration. Proposed AEGL-2 (6100 ppm, 6100 ppm, 4800 ppm, 3100 ppm, and 2000 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) values were based on no effects in rats exposed to 8000 ppm , 6 hours/day, 5 days/week for 3 months (Crouch et al., 1979). A total uncertainty factor of 3 was applied because the point of departure was a NOEL from a repeated-exposure study and use of a larger UF would have yielded AEGL-2 values in conflict with human data. Time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 when extrapolating from longer to shorter time points and 1 when extrapolating from shorter to longer time points. The 30-min value was adopted as the 10-min value. It was noted that the proposed AEGL-2 values were higher than or equal to10% of the lower explosive limit of butadiene in air (20,000 ppm).

Proposed AEGL-3 values were based on a 4-hour rat LC_{01} of 41,000 ppm. An interspecies UF of 1 was applied because the rat ventilation rate is greater than that of the human and thus the dose would be greater. An intraspecies uncertainty factor of 3 was applied because use of a larger UF would have yielded AEGL-3 values in conflict with human data and very close to proposed AEGL-2 values. Time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 when extrapolating from longer to shorter time points and 1 when extrapolating from shorter to longer time points. The 30-min value was adopted as the 10-min value. It was noted that the proposed AEGL-3 values for 10-min, 30-min, and 1-hr were higher than the lower explosive limit of butadiene in air (20,000 ppm), and the proposed 4-hour AEGL-3 is higher than 50% of the lower explosive limit of butadiene in air.

A proposed LOA of 3.7 ppm was calculated.

The committee agreed that given the significant cancer risk for this chemical, a note on that risk would be attached to the AEGL summary tables.

After discussion, a motion to accept the AEGL-3 values as proposed was made by Richard Niemier and seconded by Warren Jederburg. The motion carried (YES: 20; NO: 0; ABSTAIN: 1) (Appendix M).

A motion was then made by Bob Benson and seconded by Steve Barbee to base AEGL-2 values on a no effect level in humans exposed to 8000 ppm for 8 hours (Carpenter et al., 1944) and to support the values with the Crouch et al. (1979) data. An intraspecies uncertainty factor of 3 was applied and time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 for extrapolating from longer to shorter time points. The 30-min value was adopted as the 10-min value. Resulting AEGL-2 values were 6700 ppm, 6700 ppm, 5300 ppm, 3400 ppm, and 2700 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. The motion carried (YES: 17; NO: 4; ABSTAIN: 1) (Appendix M).

A motion to accept the AEGL-1 values as proposed was made by Susan Ripple and seconded by Bob Benson. The motion carried (YES: 18; NO: 1; ABSTAIN: 2) (Appendix M). A motion to accept the LOA as proposed was made by Richard Niemier and seconded by Richard Thomas. The motion carried unanimously by a show of hands.

Summary of AEGL Values for Butadiene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	670 ppm	670 ppm	670 ppm	670 ppm	670 ppm	Slight ocular irritation in humans (Carpenter et al., 1944)
AEGL–2	6700 ppm¶	6700 ppm¶	5300 ppm¶	3400 ppm¶	2700 ppm¶	NOEL in humans (Carpenter et al., 1944)
AEGL–3	See below*	See below*	See below*	See below*	6800 ppm¶	4-hr rat LC_{01} (Shugaev, 1969)
LOA	3.7 ppm					

*The calculated AEGL-3 values for 10-min, 30-min, and 1-hr are higher than the lower explosive limit of butadiene in air (LEL = 2% (20,000 ppm)). The calculated AEGL-3 value for 4-hr is higher than 50 f the lower explosive limit of butadiene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.
The calculated AEGL-3 values for 10-min, 30-min, 1-hr, and 4-hr are 27,000 ppm, 27,000 ppm, 22,000 ppm, and 14,000 ppm, respectively.
¶The value is higher than 10% of the lower explosive limit of butadiene in air . Therefore, safety considerations against the hazard of explosion must be taken into account.

Dimethylamine (CAS No. 124-40-3)

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

Alexander Maslennikov discussed the available data (Attachment 18). Human data are very limited for this compound. Proposed AEGL-1 values (3.3 ppm at all time points) were based on mucosal hyperemia and nasal discharge in rats and mice exposed to 100 ppm for 10-minutes (Steinhagen et al., 1982). An interspecies uncertainty factor of 10 and intraspecies uncertainty factor of 3 were proposed, and values were held constant at all time points because minor irritation is not expected to increase greatly with increasing duration. Proposed AEGL-2 values (19.3 ppm, 13.4 ppm, 10.6 ppm, 6.7 ppm, and 4.4 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on epithelial vacuolization and ulceration and inflammation in rats exposed to 175 ppm for 6 hours (Gross et al., 1987). Proposed AEGL-3 values (275.2 ppm, 190.8 ppm, 151.4 ppm, 95.4 ppm, and 62.5 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a lethality threshold of 2500 ppm in rats exposed to dimethylamine for 6 hours (Steinhagen et al., 1982). For both AEGL-2 and AEGL-3, an interspecies

uncertainty factor of 10 and intraspecies uncertainty factor of 3 were proposed, and time scaling was performed using $C^n \times t = k$, where the exponent, n, was the default value of 3 for extrapolating from longer to shorter time points and 1 for extrapolating from shorter to longer time points.

The NAC suggested that analytical methods be described in more detail in the TSD and that a table be included for the Stienhagen et al., (1982) study showing effects at each exposure level. A suggestion was made that the CIIT scientists (Steinhagen et al) be contacted to determine why a 2-day observation period was utilized, rather than the customary 14-day period. It was also noted that the IDLH has been decreased from 2000 ppm to 500 ppm.

A motion was made by Marc Ruijten and seconded by Richard Thomas to adopt Draft Provisional AEGL-3 values as proposed except that inter- and intraspecies uncertainty factors of 3 each be applied (total UF= 10) because dimethylamine is a highly-reactive irritant. Also, the 30-min AEGL-3 value will be adopted as the 10-min value because the POD was 6 hours. The Mazenska data should be used as support. The motion carried (YES: 14; NO: 5; ABSTAIN: 0) (Appendix N). A motion was then made by Marc Ruijten and seconded by Richard Niemier to adopt AEGL-1 values as proposed except that inter- and intraspecies uncertainty factors of 3 each be applied (total UF= 10) because dimethylamine is a highly-reactive irritant. Data showing no effects at 50 and 100 ppm in chronic studies should be used as support. The motion carried (YES: 17; NO: 2; ABSTAIN: 2) (Appendix N).

NAC members should send any other comments and suggestions to the chemical manager and the staff scientist and chemical manager will work together to revise the TSD and derive AEGL-2 values. The TSD will be discussed at a future meeting and the draft provisional values may be reaffirmed at this time.

Summary of Draft Provisional AEGL Values for Dimethylamine

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm	Slight irritation in rats and mice (Steinhagen et al., 1982)
AEGL–2	-	-	-	-	-	-
AEGL–3	570 ppm	570 ppm	450 ppm	290 ppm	190 ppm	Lethality threshhold in rats (Steinhagen et al., 1982)

Ethyl Mercaptan(CAS No. 75-08-1)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

Cheryl Bast discussed the human and animal data available for derivation of AEGL values (Attachment 19). The proposed AEGL-1 values were based on a NOEL for irritation in rabbits exposed to 10 ppm for 20 minutes (Shibata, 1966b). Uncertainty factors of 3 each were applied to account for interspecies and intraspecies variability, and were considered sufficient because use of the full factor of 10 for either interspecies or intraspecies variability would yield AEGL-1 values #0.3 ppm which is inconsistent with the available human data. A level of distinct odor awareness for ethyl mercaptan was 0.012 ppm calculated.

No robust data consistent with the definition of AEGL-2 were available. Therefore, the proposed AEGL-2 values for ethyl mercaptan were based upon a 3-fold reduction in the AEGL-3 values; this was considered an estimate of a threshold for irreversible effects and is appropriate because of the steep concentration-response curve for ethyl mercaptan toxicity. Also, the ratio of AEGL-3:AEGL-2 values (data derived) for the structural analog, methyl mercaptan, may be used to support the AEGL-2 values for ethyl mercaptan.

Proposed AEGL-3 values were based on a calculated LC_{01} (2250 ppm; Litchfield & Wilcoxon method) in mice exposed to ethyl mercaptan for 4 hours (Fairchild and Stokinger, 1958). The LC_{01} was used as the point of departure because this same approach was utilized in the derivation of AEGL values for the structurally and mechanistically similar, methyl mercaptan. An intraspecies uncertainty factor of 3 was applied and is considered sufficient due to the steepness of the lethal response curve which implies limited individual variability. An interspecies uncertainty factor of 3 was also be applied because the limited data suggest that the mouse is the most sensitive species. Time scaling was performed by $c^n \times t = k$, where the exponent, n, were default values of n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time point. The 30-minute AEGL-3 value is adopted as the 10-minute value.

After discussion, it was moved by Nancy Kim and seconded by George Rodgers that the AEGL-1 values be accepted as proposed. The motion carried (YES: 20; NO: 0; ABSTAIN: 1) (Appendix O). A motion was then made by Bob Benson and seconded by Ernie Falke to accept the AEGL-3 values as proposed. The motion carried (YES: 16; NO: 0; ABSTAIN: 5) (Appendix O). [Concern was expressed regarding the calculation of the LC_{01} via the Litchfield/Wilcoxon method vs. the EPA BMD software. The values presented at the meeting have been re-calculated and verified: LC_{01} from Litchfield/Wilcoxon method = 2250 ppm; $BMCL_{05}$ = 1545 ppm; BML_{05} = 2135 ppm; $BMCL_{01}$ = 1269 ppm; BMC_{01} = 1920 ppm.] A motion was then made by Marc Ruijten and seconded by Steve Barbee to accept AEGL-2 values as proposed. The motion carried (YES: 17; NO: 3; ABSTAIN: 1) (Appendix O).

Marc Ruijten then presented new odor data, allowing for a more precise LOA calculation. A motion was made by Marc Ruijten and seconded by Susan Ripple to accept an LOA of 0.00014 ppm. The motion carried unanimously by a show of hands (Appendix O).

Summary of AEGL Values for Ethyl Mercaptan						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm	NOEL for irritation in rabbits (Shibata, 1966b)
AEGL–2	150 ppm	150 ppm	120 ppm	77 ppm	37 ppm	3-fold reduction of AEGL-3 values
AEGL–3	450 ppm	450 ppm	360 ppm	230 ppm	110 ppm	LC_{01} in mice (Fairchild and Stokinger, 1958)
LOA	0.00014 ppm					

Nitrogen Mustards
(HN1: CAS No. 538-07-8)
(HN2: CAS No. 51-75-2)
(HN3: CAS No. 555-77-1)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Richard Thomas, INTERCET, Inc.

Bob Young discussed the human and animal data available for derivation of AEGL values for nitrogen mustards (Attachment 20). During deliberations, three issues were identified: 1) the possibility of an empirically derived scaling exponent, *n*, for $C^n \times t = k$, 2) justification for the development of AEGLs for nitrogen mustards, and 3) data quality and availability of key studies. This TSD was tabled and AEGL development for nitrogen mustards will be revisited at a future meeting.

OTHER ISSUES/PRESENTATIONS

Application of AEGLs

John Morawetz presented a proposed statement concerning the application/use of AEGL values (Attachment 21). It was suggested that this statement be posted on the EPA website and included in the TSDs. A motion was made by John Morawetz and seconded by Bob Benson to adopt the language in Attachment 21. The motion carried (YES: 15; NO: 0; ABSTAIN: 1) (Appendix P).

Rewording of AEGL Definition

The U.S. EPA AEGL web page originally had a two-sentence description of AEGLs. John Morawetz suggested changes to the web page definition, particularly a more accurate depiction of "once-in-a lifetime"exposures (Attachment 22). The definition originally read,

> *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.*

At the April 2004, meeting, the committee discussed including the statement that "AEGLs are intended to describe the risk resulting from once in a lifetime or rare exposure to airborne chemicals" and that "Definition: Acute exposures are single, non repetitive exposures."

Iris Camacho discussed the changes adopted to the AEGL definition after collecting formal vote on September 23, 2004. The website definition approved in September 2004 reads,

> **Acute Exposure Guideline Levels, or AEGLs, 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 national and local authorities, as well as private companies, deal with emergencies involving spills or other catastrophic exposures.*
>
> **Acute exposures are single, non repetitive exposures for not more than 8 hours.*

After discussion, a motion was made by John Morawetz and seconded by Ernie Falke to adopt the above language for the web site. The motion carried (YES: 17; NO: 0; ABSTAIN: 0) (Appendix Q).

SOP PBPK White Paper

Jim Dennison presented information concerning the use of PBPK modeling in AEGL value development ("The White Paper") (Attachment 23). After approval by the NAC and COT AEGL subcommittee, this guidance may become part of the revised SOP. After discussion, George Rusch requested that NAC members send any comments to Marquea King within 4-6 weeks after the meeting so that the PBPK White Paper may be revised and presented at the April, 2005, NAC meeting.

ADASHI (Automated Decision-Aid System for Hazardous Incidents)

Jim Genovese and Alex Menkes (Edgewood Chemical Biological Center) presented The ADASHI system (Attachment 24). This system has been in existence for seven years, and may be used to track hazards over time and space. Thus, exposure may be predicted alllowing for hazard and/or casualty assessment.

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-36: April 12-14, 2005, Research Triangle Park, NC
NAC/AEGL-37: June 13-15, 2005, Washington DC

Closed Session: A closed session of the NAC was conducted to discuss the Gallup Organization results of a member survey.

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

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-35 Meeting Agenda
Attachment 2. NAC/AEGL-35 Attendee List
Attachment 3. Response to Federal Register comments for acrolein
Attachment 4. Federal Register comments for chloroform
Attachment 5. RIVM report on use of developmental toxicity data for setting acute limit values
Attachment 6. Response to Federal Register comments for dimethylformamide
Attachment 7. Response to Federal Register comments for epichlorohydrin
Attachment 8. Response to Federal Register comments for nitrogen dioxide
Attachment 9. Response to Federal Register comments for peracetic acid
Attachment 10. Response to Federal Register comments for trichloroethylene
Attachment 11. Response to COT comments for perchloromethyl mercaptan

LIST OF APPENDICES

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-35
December 13-15, 2004

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

Metro: Judiciary Square (Red Line)

AGENDA

Monday, December 13, 2004

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-34 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15	Discussion of Public Comments: Acrolein, Chloroform, Epichlorohydrin, n,n-Dimethylformamide, Nitrogen dioxide, Peracetic acid, Trichloroethylene
12:00	Methylene chloride: Validation of draft provisional values (Bob Benson/Peter Bos)
12:20	Update on Vinyl Acetate (Richard Thomas/ Claudia Troxel)
12:30 p.m.	Lunch
1:30	Review of Chloroacetaldehyde (Marinelle Payton/Peter Bos)
2:30	Revisit of Perchloro methylmercaptan- COT Comments (Susan Ripple/Claudia Troxel)
3:00	Break
3:15	Review of Propionaldehyde (Marinelle Payton/Peter Bos)
4:15	Discussion of PBPK SOP White Paper and Revisit of Tetrachloroethylene (Bill Bress/Claudia Troxel/ Jim Dennison)
5:30	Adjourn for the day

Tuesday, December 14, 2004

8:30 a.m.	Review of Biphenyl (Richard Thomas/Dana Glass)
9:30	Review of Butadiene (Al Feldt/Peter Bos)
10:30	Break
10:45	Review of Dimethylamine (Ernie Falke/Alexander Maslennikov)
12:30p.m.	Lunch
*1:30**	*Review of Methyldichlorosilane and Methylchlorosilane (Ernie Falke/Cheryl Bast)*
*2:30**	*Review of Hexafluoroacetone (Paul Tobin/Bob Young)*
3:30	Break
3:45	Automated Decision Aid System for Hazardous Incidents (Jim Genovese/Art Stuempfle/Alex Menkes)
5:30	Adjourn for the day

Wednesday, December 15, 2004

8:00 a.m.	Language Issues: 1) Use of AEGLs; 2) Webpage (John Morawetz/George Rusch/Ernie Falke)
8:30	Review of Ethyl Mercaptan (Iris Camacho/Cheryl Bast)
9:45	Break
10:00	Review of Nitrogen Mustards (Richard Thomas/Bob Young)
11:30	Administrative matters- Closed Session: Gallup Organization Results of Member Survey
12:00 noon	Adjourn meeting

**In the event that the meeting is behind schedule, methyldichlorosilane, methyldichlorosilane, and hexafluoroacetone may be deferred to NAC-36 (Spring, 2005).*

ATTACHMENT 2

12/13 - 12/15 2004

(PLEASE CHECK NAME AND INFORMATION)

ATTENDEES

NATIONAL ADIVSORY COMMITTEE FOR ACUTE EXPOSURE GUIDELINE LEVEL
Meeting

RETURN TO PAUL TOBIN

December 13-15, 2004
FPB Room C-5515, Seminar Room 1A and 1B

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ACROLEIN: RESPONSE TO FR08 COMMENTS

ORNL Staff Scientist: Cheryl Bast
Chemical Manager: Robert Snyder

AEGL-3:

COMMENT: Ernest Falke

The 1 hour AEGL-3 should be 1.4 ppm, not 1.5 ppm. The POD was 14 ppm for 1 hour with a total UF of 10. 14/10 is 1.4. Page A-4 should be revised accordingly as well as the text.

RESPONSE:

Page A-4 will be corrected. The values given in the text and tables are correct (1.4 ppm).

AEGL-2:

COMMENT: George Alexeeff

The description of the starting point for AEGL-2 requires clarification. Page 23 states "a 10-25% decrease in respiratory rate along with moderate to severe eye and nose irritation were observed in human subjects. The threshold for these effects is 0.3 ppm." The SOPs indicate that the starting point for the AEGL-2 should be the the highest concentration that does not produce the AEGL-2 effect. The document needs to identify the AEGL-2 effect of concern, that is, the LOAEL for AEGL-2. Next, it needs to be clarified if 0.3 ppm represents the NOAEL for the AEGL-2 effect. Currently the document suggests the 0.3 ppm causes severe eye irritation, i.e., an AEGL-2 effect. If that is the case, I suggest that the LOAEL be adjusted by a factor of 2 to estimate the NOAEL, prior to adding the uncertainty factor of 3 to protect for sensitive individuals.

RESPONSE:

Clarify text as follows:

A 10% decrease in respiratory rate was noted in humans exposed to 0.3 ppm acrolein for 1 hour; whereas, a 25% decrease in respiratory rate was noted in humans exposed to 0.6 ppm for 1 hour (Weber-Tschopp, et al. 1977). According to ASTM (1991), decreases in respiratory rate in the range of 12 to 20% correspond to slight irritation, and decreases in respiratory rate in the range of 20 to 50% correspond to moderate irritation. The AEGL-2 will be based on the 10% decrease in respiratory rate in healthy human subjects exposed to 0.3 ppm for 1 hour. This is considered a NOAEL for moderate irritation.

ASTM. (American Society for Testing and Materials). 1991. Standard Test Method for estimating sensory irritancy of airborne chemicals. Method E981, Volume 11.04, p. 610-619. ASTM Philadelphia, PA.

The AEGL-2 POD of 0.3 ppm, with no modifying factor, is also supported by the fact that if application of a MF of 2 would yield AEGL-2 values (0.22 ppm for 10-min, 0.09 ppm for 30-min, and 0.05 ppm for 1-, 4-, and 8-hrs) in the range of or below occupational guidelines and where only minor irritation was noted in controlled human studies.

AEGL-1:

COMMENT: Robert Sills, Michigan Department of Environmental Quality

The proposed AEGL-1 values, based on a 5-minute irritancy effect, are identical for all averaging times (10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours). The justification provided is, "...because minor irritancy is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect."

RESPONSE:

AEGL-1 values are often held constant across time for sensory irritants as described in the SOP (Section 2.7.7):

"In the case of certain sensory irritants, the AEGL values may be constant across all AEGL time periods, because this endpoint is considered a threshold effect, and prolonged exposure will not result in an enhanced response. In fact, individuals may adapt or become inured to sensory irritation provoked by exposure to these chemicals over these exposure periods such that the warning properties are reduced."

COMMENT: Robert Sills, Michigan Department of Environmental Quality

The key study was conducted with healthy adult subjects, and the uncertainty factor applied for the protection of sensitive subpopulations was 3 rather than the normal default of 10.

RESPONSE:

An intraspecies UF of 3 is typically applied for minor irritation.

COMMENT: Robert Sills, Michigan Department of Environmental Quality

A key human exposure study by Darley et al. (1960) is not cited or described in the AEGL-1 derivation; it should be reviewed and included.

RESPONSE:

The following study description may be included in the TSD:

Thirty-six students (26 male and 10 female) were exposed to 0, 0.06, 1.3-1.6, or 2.0-2.3 ppm acrolein through an eye mask for 5 minutes (Darley et al., 1960). A 16-cubic foot glass and aluminum fumigation chamber was constructed and operated as a stirred flow reactor. The chamber was set up in a greenhouse in order to study damage to plants from acrolein exposure. Three eye irritation booths were constructed adjacent to the plant exposure chamber. The exhaust air from the chamber was run in an all glass system to a manifold and then through three air flow lines, one to each eye exposure booth. The end of each line was connected to a loose-fitting plastic face mask. Acrolein was diluted in water and the mixture dispensed from a syringe into a stream of oxygen. Concentrations were determined by absorbing the vapors in a buffered semicarbazide hydrochloride solution and reading the absorbance on a spectrophotometer. During exposure, the subjects wore activated carbon respirators so they breathed clean air and only the eyes were exposed to the acrolein. Each student recorded the degree of irritation every 30 seconds during the 5-minute exposure. Irritation was rates as none (score 0), medium (score 1), or severe (score 2). The maximum value recorded by a subject during a test was used as the response for that experimental session. Average maximum irritation scores are as follows:

Acrolein Concentration	Average maximum irritation Scores
0 ppm (filtered air)	0.361
0.06 ppm	0.471
1.3-1.6 ppm	1.182
2.0-2.3 ppm	1.476

COMMENT: Robert Sills, Michigan Department of Environmental Quality

The human inhalation irritation LOAEL from Darley et al. (1960) was 0.06 ppm for 5 minutes. The proposed AEGL-1 is based upon a different study of human inhalation with an acute 5 minute) irritancy LOAEL of 0.09 ppm. The Darley et al. (1960) study provides a lower LOAEL and should be accounted for in AEGL-1 development.

RESPONSE:

From the data presented in the Darley et al (1960), there is no clear concentration-response with regard to irritation at the 0.06 ppm level. The filtered air irritation score (0.361) and 0.06 ppm acrolein score (0.471) are both <0.5, where 0 is defined as "no irritation" and 1 is defined as "medium irritation." Thus, it may be concluded that both the air control and 0.06 ppm may have caused "slight irritation."

Also, the Weber-Tschopp et al. (1977) study is a more robust study in that the protocol and analytical methods are better described. Also, the Weber-Tschopp study is actually an inhalation exposure, not just an ocular exposure. It is therefore more appropriate to use the Weber-Tschopp study as the key reference. The Darley study may be useful as support (see below).

COMMENT: George Alexeeff

I would like to raise concerns regarding the justification for the AEGL-1 values recommended by the AEGL Committee for Acrolein. The AEGL-1 value is based on the Weber-Tschopp et al., 1977 study. Page 22 of the document states that ocular, nasal, and throat irritation were reported in healthy human volunteers exposed to 0.09 ppm acrolein. Further, page 23 states: "eye irritation and 'annoyance'/discomfort were observed in human subjects. The threshold for these effects is 0.09 ppm." The statements on page 22 and 23 appear to contradict each other. Page 22 indicates the effects occurred at 0.09 ppm, i.e., a LOAEL, while page 23 states it was the threshold for the effects, i.e., a NOAEL. I request the document follow the NAC/AEGL Standing Operating Procedures (SOPs) and specify whether the effect was a NOAEL or LOAEL. Further, if the effect is considered to be a LOAEL, I suggest that the LOAEL be adjusted by a factor of 2 to estimate the NOAEL, prior to adding the uncertainty factor of 3 to protect for sensitive individuals. As indicated in the AEGL-1 definition and the SOPs, the starting point should be the level that does not produce the AEGL-1 effect.

RESPONSE:

Weber-Tschopp et al (1977) refer to the 0.09 ppm acrolein concentration as the "threshold" for annoyance and ocular irritation. However, 0.09 ppm is the lowest concentration where effects were observed (LOAEL).

The Darley et al. (1960) study suggests no significant increase in ocular irritation at 0.06 ppm.

Therefore, we may use the 0.09 ppm concentration as the POD and use the 0.06 ppm concentration to support NO modifying factor.

Revise TSD follows:

The AEGL-1 values will be based on eye irritation and "annoyance"/discomfort observed in human subjects exposed to 0.09 ppm acrolein (Weber-Tschopp et al., 1977). An intraspecies uncertainty factor of 3 will be applied and is considered sufficient because minor ocular contact irritation is unlikely to vary greatly between humans. The values will be held constant across time for the 10-min, 30-min, 1-hr, 4-hr, and 8-hr time points because minor irritancy is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect.

A modifying factor may normally be applied to account for the use of a LOAEL; however, no significant irritation was noted in humans exposed to 0.06 ppm acrolein (Darley et al., 1960). The derived AEGL-1 values (0.03 ppm) are 2-fold below the concentration showing no irritation and are thus considered protective.

ATTACHMENT 4

oppt.ncic@epa.gov

October 7, 2004

Attention: Docket Number OPPT-2004-0079
OPPT Document Control Office
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1201 Constitution Avenue, N.W.
Washington, DC 20460-0001

Docket control # OPPTS—2004-0079: chloroform AEGL-2 values

I would like to request clarification of the AEGL-2 description and calculation. The document states on page 26 that "chloroform at 30 ppm induced some evidence of embryotoxicity and fetotoxicity while the 100- and 300-ppm exposures caused significant toxicity (Table 5). The investigators concluded that exposure to 30 ppm chloroform produced minor effects on the embryo and fetus, exposure to 100 ppm was highly embryotoxic and fetotoxic, and that exposure to 300 ppm was embryocidal as well as highly embryotoxic and fetotoxic." On page 7 the document states: "The AEGL-2 values for chloroform were based upon fetotoxicity and embryolethality in rats (Schwetz et al., 1974) resulting from exposure of dams to 100 ppm, 7 hours/day on gestation days 6-15. For AEGL-2 development, an assumption was made that the effects could be caused by only a single 7-hr exposure." Based on the discussion in the document, it is clear that 100 ppm represents a LOAEL for fetotoxicity and embryolethality. As indicated in our SOPs, the AEGL-2 is to be based on the NOAEL for the AEGL-2 effect. For this reason the starting point should be 30 ppm and the AEGL-2 values should be adjusted accordingly. The next statement on page 7 is a *non sequiter*: "Because available data on metabolism and kinetics indicate that rodents are more sensitive than humans to the toxic effects of chloroform, an interspecies variability uncertainty factor was not applied." Metabolism and kinetics do not provide information of tissue sensitivity and response. Interspecies differences are divided into pharmacokinetic and pharmacodynamic differences. Metabolism and kinetics cannot provide information on the pharmacodynamic differences between rats and humans. Standard assumptions in risk assessment reduce the interspecies uncertainty factor from 10 to 3 when pharmacokinetics is taken into account. There are some concerns that humans may be more susceptible to developmental toxicity than rats based on the 33-fold increase in sensitivity to thalidomide.

I request that the Committee consider these recommendations and revise the AEGL documents accordingly.

Sincerely,

George V. Alexeeff, Ph.D., D.A.B.T.