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

March 3-5, 2008

Meeting-45 Highlights

Hilton- Old Town Alexandria
1867 King Street
Alexandria, VA

INTRODUCTION

Ernie Falke discussed the chemical planning for the next AEGL meetings. The June, 2008, meeting agenda will include approximately 15 chemicals. Five chemicals on the priority list do not have enough data to develop numbers and the limited data are thought to be insufficient to derive AEGL values by analogy. Four organophosphate chemicals will be discussed in June. Richard Niemeier requested that the Department of Homeland Security (DHS) list be consulted. Ernie Falke indicated that Paul Tobin has already looked at the list. Richard stated that the DHS list was developed mainly for water threats. The FBI list has TCDD or dioxin as a concern chemical and there was a brief discussion about deriving AEGL values for TCDD. Ricin is another chemical that the committee may review in the future. Development of AEGLs for radionuclides was briefly discussed but dismissed as the committee does not have the expertise to evaluate radiological chemicals, and there is already guidance on how to deal with these substances. The December, 2008, meeting will include approximately 10 chemicals from the priority list. At the pace that the committee is reviewing chemicals, the current priority list may be finished by December, 2008.

Ernie Falke announced that the next NAS/AEGL/COT (NAS-18) subcommittee meeting will be held May 12-14, 2008, in Washington, D.C. He then distributed the lists of candidate chemicals for NAS-18 and NAS-19 and asked for NAC member volunteers to present and defend the TSDs to the COT subcommittee. Volunteers should let Ernie know by the end of the current NAC meeting.

Iris Camacho will take Ernie's place as a voting member on the NAC, effective at NAC-46 (June, 2008). Ernie will continue to attend and participate in NAC meetings and coordinate the overall effort.

The draft NAC/AEGL-44 meeting highlights were reviewed. George Woodall pointed out that rabbits are not rodents; thus, the n,n-dimethylformamide discussion needs to be corrected to reflect this fact. Also, Gail Chapman's name is misspelled in the chloropicrin discussion. A motion was made by John Hinz and seconded by Calvin Willhite to accept the minutes as proposed with the

aforementioned corrections. The motion passed unanimously by a show of hands (Appendix A). The Final NAC/AEGL-44 meeting highlights are attached (Appendix B).

The highlights of the NAC/AEGL-45 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-45 Agenda.

NO DATA CHEMICAL

Ethylphosphonothioic dichloride (CAS No. 1498-40-4)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA; George Rusch, Honeywell Corp.

There are no data currently available for development of AEGL values for ethylphosphonothioic dichloride. This chemical was placed in holding status.

CHEMICAL REVISITS/STATUS UPDATES

1,1,1-Trichloroethane (CAS No. 71-55-6)

Staff Scientist: Sylvia Talmage, ORNL; Jim Dennison, Century Environmental Hygiene, LLC
Chemical Manager: Bob Benson, U.S. EPA

Sylvia Talmage and Jim Dennison updated the NAC on the status of 1,1,1-trichloroethane (Attachment 3). Available models did not address the needs of AEGL development. Jim worked on improving the models and presented some preliminary results for AEGL-2 development. Jim and Sylvia noted that data are sparse for AEGL-2 development. Data for AEGL-3 development/time-scaling and additional data for AEGL-2 development will be run in the improved model, and results will be presented at NAC-46 (June, 2008).
.

Tetrachloroethylene (CAS No. 127-18-4)

Staff Scientist: Claudia Troxel, CMTox; Jim Dennison, Century Environmental Hygiene, LLC
Chemical Manager: Bob Benson, U.S. EPA

This chemical was deferred until NAC-46 (June, 2008) for PBPK modeling.

REVIEW of PRIORITY CHEMICALS

Nitrogen trioxide (CAS No. 10544-73-7)
Nitrogen tetroxide (CAS No. 10544-72-6)

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

Carol Wood summarized the data in the TSD (Attachment 4), and explained that nitrogen dioxide is interim status and is currently under review by the AEGL/COT subcommittee. Nitrogen tetroxide and nitrogen trioxide are draft status, and were added to the nitrogen dioxide TSD to create the TSD for nitrogen oxides. This approach was used because chemical-specific data for nitrogen trioxide and nitrogen tetroxide are very sparse. NO2 exists as an equilibrium mixture of NO2 and N2O4 but the dimer is not important at ambient concentrations. The two compounds are phase-related forms with N2O4 favored in the liquid phase and NO2 favored in the gaseous phase. As a result when N2O4 is released it vaporizes and dissociates into NO2, making it nearly impossible to generate a significant concentration of N2O4 at atmospheric pressure and ambient temperatures, without generating a vastly higher concentration of NO2. Almost no inhalation toxicity data are available on N2O4 or another oxide of nitrogen, nitrogen trioxide (N2O3). Thus, the proposed AEGL values were developed based on data for NO2 and were considered applicable to all nitrogen oxides. After significant discussion on environmental chemistry of the nitrogen oxides, a motion was made by Marcel van Raaij and seconded by John Hinz to adopt AEGL-1, AEGL-2, and AEGL-3 values for N2O4. The NO2 values were adopted as the N2O4 values on a mg/m^3 basis. The chemical-specific values from conversion to ppm will also be provided in the TSD. The motion passed (YES: 19; NO: 0; ABSTAIN: 2; Appendix C). A motion was then made by Richard Niemeier and seconded by Deiter Heinz to place N2O3 in holding status and remove it from the TSD because of a lack of chemical reaction data. The motion passed unanimously by a show of hands (Appendix D). The text in the TSD should be revised to indicate that NO2 represents the major component of the reaction.

Summary of AEGL Values for Nitrogen Tetroxide						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	0.94 mg/m^3 0.25 ppm	0.94 mg/m^3 0.25 ppm	0.94 mg/m^3 0.25 ppm	0.94 mg/m^3 0.25 ppm	0.94 mg/m^3 0.25 ppm	Analogy to NO2
AEGL-2	38 mg/m^3 10 ppm	28 mg/m^3 7.6 ppm	23 mg/m^3 6.2 ppm	15 mg/m^3 4.1 ppm	13 mg/m^3 3.5 ppm	Analogy to NO2
AEGL-3	64 mg/m^3 17 ppm	47 mg/m^3 13 ppm	38 mg/m^3 10 ppm	26 mg/m^3 7.0 ppm	21 mg/m^3 5.7 ppm	Analogy to NO2

Ethyl Benzene (CAS No. 100-41-4)

Staff Scientist: Carol Wood, ORNL

Chemical Manager: John Hinz, U.S. Air Force

Carol Wood summarized the data in the TSD and presented a brief review of the history of this TSD (Attachment 5). Ethyl benzene was originally addressed by the NAC in September, 2006 at which time industry said they had unpublished data. Those data were incorporated into the second draft which was brought to the NAC in December, 2006 at which time it was decided to look at PBPK modeling. At the December 2006 meeting, the NAC discussed and decided upon the key studies and points of departure to use in the model. These were communicated to industry and the model was run. However, the model produced AEGL 2 values higher than AEGL 3 values. The basis for AEGL 2 was a 5 day exposure so the model calculated an area under the curve based on a cumulative exposure while the AEGL 3 values were based on peak blood concentration. Because the AEGL-2 values cannot be higher than AEGL-3 values, the proposed AEGL-2 and AEGL-3 values were based on the NAC chosen PODs and calculated using the ten Berge equation. Proposed AEGL-1 values (10 ppm at all time points) were based on a NOEL for irritation in humans exposed to 100 ppm for 8-hours with an intraspecies UF of 10. Proposed AEGL-2 values (46 ppm for 10- and 30-min, 37 ppm for 1-hr, 23 ppm for 4-hr and 18 ppm for 8-hr) were based on ototoxicity in female rats exposed to 550 ppm, 8 hr/day for 5 days. Proposed AEGL-3 values (150 ppm for 10- and 30-min, 120 ppm for 1-hr, 76 ppm for 4-hr and 50 ppm for 8-hr) were based on the highest non-lethal concentration in rats (2000 ppm for 6 hr). For both AEGL-2 and AEGL-3 values, scaling across time used the default exponents of n=3 when scaling from longer to shorter times and n=1 when scaling from shorter to longer times. A total UF of 30 (3 for interspecies and 10 for intraspecies) was proposed for both AEGL-2 and AEGL-3. The discussion focused on the use of PBPK modeling for AEGL-2 and AEGL-3 values and the endpoints used for modeling. The endpoint of ototoxicity for AEGL-2 values did not receive the support of the majority of the committee members as it was unclear if an acute exposure would result in ear damage.

A motion was made by John Hinz and seconded by Dieter Heinz to adopt AEGL-1 values of 33 ppm at all time points. The AEGL-1 derivation retains the the key study and endpoint but decreases the intraspecies UF from 10 to 3 because the endpoint is irritation and >3-fold differences would be not be expected among human populations. The motion passed (YES: 17; NO: 0; ABSTAIN: 4; Appendix E).

A motion was made by John Hinz and seconded by Dieter Heinz to adopt AEGL-3 values of 4700 ppm for 10-min, 2600 ppm for 30-min, 1800 ppm for 1-hr, 1000 ppm for 4-hr and 910 ppm for 8-hr based on PBPK modeling with the POD of 2000 ppm for 6 hours (no death or clinical signs in rats). The intraspecies uncertainty factor was decreased from 10 to 3 because lethality results from CNS depression and CNS effects are typically within 2-3 fold difference among the human populations. PBPK modeling allowed reducing the interspecies UF from 10 to 1. Data from xylenes and toluene supported the modeling of 10-min AEGL-3 values and the revised TSD will have a supporting statement of this approach based on xylene and toluene data. The motion passed (YES: 18; NO: 0; ABSTAIN: 2; Appendix E).

Finally, the committee deferred action on AEGL-2 values. PBPK modeling will be run with a CNS endpoint of 1500 ppm for 4-hr (Molnar et al., 1986). Jim Dennison will contact industry and request

to run the model with new information. A focused discussion on the ethyl benzene AEGL-2 values will be scheduled for NAC-46 (June, 2008).

Summary of AEGL Values for Ethyl Benzene						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	33 ppm	33 ppm	33 ppm	33 ppm	33 ppm	NOEL for irritation in humans (Bardodej and Bardodejova, 1961)
AEGL-2						Deferred
AEGL-3	4700 ppm	2600 ppm	1800 ppm	1000 ppm	910 ppm	Highest non-lethal concentration in rats (Andersson et al., 1981)

Cyanogen (CAS No. 460-19-5)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Glenn Leach, U.S. Army

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for cyanogen (Attachment 6). Proposed AEGL-1 values (2.7 ppm for 10- and 30-min, and 0.90 ppm for 1-, 4-, and 8-hr) were based on a NOEL for irritation in humans (8 ppm for 6 minutes) (McNerney and Schrenk, 1960). Ocular and nasal irritation was noted at the next highest concentration tested (16 ppm). An intraspecies uncertainty factor of 3 was applied because contact irritation is a portal of entry effect and is not expected to vary widely between individuals. An interspecies uncertainty factor of 1 was applied because the study was conducted in humans. Time scaling was not applied in the development of the AEGL-1 values. The critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and is not likely to increase with duration of exposure. However, because of the lack of human data beyond 8-minutes and because of the potential for a systemic effect from the cyanide metabolite, a modifying factor of 3 was applied for 1-, 4-, and 8-hour exposure time points. Proposed AEGL-2 values (50, 15, 7.0, 3.7, and 3.7 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively) were based on a 3-fold reduction in AEGL-3 values. The approach was justified by a steep concentration-response curve. Proposed AEGL-3 values (150, 45, 21, 11, and 1 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively), were based on the threshold for lethality at each AEGL-3 exposure duration calculated from rat lethality data using the probit-analysis based dose-response program of ten Berge (2006). The threshold for lethality was set at the LC_{01}. The data indicated a time-scaling value of 0.904 ($C^{0.90} \times t = k$). These calculated values were used as the basis for the 10-minute, 30-minute, and 1-hour AEGL-3 values. A modifying factor of 2 was applied to the 1-hour AEGL-3 value to derive the 4- and 8-hour AEGL-3 values. An intraspecies uncertainty factor of 3 was proposed and considered sufficient due to the steep concentration-response. An interspecies

uncertainty factor of 3 was also proposed because there application of a total uncertainty factor of 30 would yield AEGL-3 values inconsistent with the overall data base.

After discussion, a motion was made by Marcel van Raaij and seconded by Dieter Heinz to adopt AEGL-3 values based on experimental concentrations causing no deaths in rats (McNerney and Schrenk, 1960) as points-of–departure for the 10-minute, 30-minute, and 1-hour AEGL-3 values. The 7.5-minute exposure to 2000 ppm was used as the POD for the 10-minute AEGL-3 value; the 7.5 minute value was scaled to 10-minutes using the $C^n \times t = k$ equation, where n = 1 (default). The 30-minute exposure to 500 ppm was used as the POD for the 30-minute AEGL-3 value, and the 1-hour exposure to 250 ppm was used as the POD for the 1-hour AEGL-3 value. A modifying factor of 2 was applied to the 1-hour AEGL-3 value to derive the 4- and 8-hour AEGL-3 values. Using the $C^n \times t = k$ equation, where n = 1, would yield 4- and 8-hour AEGL-3 values inconsistent with repeated-exposure data in both monkeys and rats. Inter- and intraspecies uncertainty factors remained as proposed. The motion also included deriving AEGL-2 values through a 3-fold reduction of AEGL-3 values. The motion passed (YES: 19; NO: 0; ABSTAIN: 0; Appendix F). A motion was then made by John Hinz and seconded by Glenn Leach to adopt hydrogen cyanide AEGL-1 values as AEGL-1 values for cyanogen. This approach is supported by cyanogen irritation in humans (McNerney and Schrenk, 1960). The NOEL for irritation in humans exposed to cyanogen for 6 minutes was 8 ppm. Ocular and nasal irritation were noted at the next highest concentration tested (16 ppm). Application of an intraspecies uncertainty factor of 3 (applied because contact irritation is a portal of entry effect and is not expected to vary widely between individuals) applied to the 8 ppm NOEL, results in a threshold for irritation of 2.7 ppm. (An interspecies uncertainty factor of 1 would also be applied because the study was conducted in humans). Time scaling of this 2.7 ppm irritation threshold would not be appropriate, because the critical effect (ocular and nasal irritation) is a function of direct contact with the cyanogen vapors and not likely to increase with duration of exposure (NRC, 2001). However, because of the lack of human data beyond 8-minutes and because of the potential for a systemic effect from the cyanide metabolite, the hydrogen cyanide AEGL-1 values will be adopted as AEGL-1 values for cyanogen. The AEGL-1 values are all below the cyanogen irritation threshold of 2.7 ppm and are thus protective for both irritation and potential systemic cyanide effects. The motion passed (YES: 20; NO: 0; ABSTAIN: 1; Appendix F).

Summary of AEGL Values for Cyanogen

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	2.5 ppm 2.8 mg/m^3	2.5 ppm 2.8 mg/m^3	2.0 ppm 2.2 mg/m^3	1.3 ppm 1.4 mg/m^3	1.0 ppm 1.1 mg/m^3	Cyanide AEGL-1 values (NRC, 2002) adopted as AEGL-1 values for cyanogen
AEGL–2	50 ppm 100 mg/m^3	17 ppm 36 mg/m^3	8.3 ppm 17mg/m^3	4.3 ppm 9.0 mg/m^3	4.3 ppm 9.0 mg/m^3	One-third the AEGL-3 Values

AEGL–3	150 ppm 320 mg/m^3	50 ppm 100 mg/m^3	25 ppm 53 mg/m^3	13 ppm 27 mg/m^3	13 ppm 27 mg/m^3	Concentrations causing no lethality in rats (McNerney and Schrenk, 1960)

n-Butyl isocyanate (CAS No. 111-36-4)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Bob Young summarized the data set for n-butyl isocyanate (Attachment 7). Proposed AEGL-1 values for *n*-butyl isocyanate were based on the lower range (0.005 to 0.01 ppm) for occupational exposures producing noticeable ocular irritation (Du Pont, 1986). Although the lower range may be representative of more sensitive individuals, it is assumed that these workers were familiar with and at least somewhat accustomed to the irritant effects of *n*-butyl isocyanate. For this reason and because the critical effect was "noticeable" irritation, a 3-fold uncertainty adjustment was applied for development of the AEGL-1 values. The critical effect and point-of-departure (POD) are from human exposure findings, therefore no interspecies uncertainty factor was applied. Because *n*-butyl isocyanate is a contact irritant, the ocular irritation is not dependent upon exposure duration and no time scaling was considered necessary for the AEGL-specific exposure periods.

Proposed AEGL-2 values were based on an industrial hygiene report (DuPont, 1986) that noted exposure to 50 ppb (0.05 ppm) for a nonspecified duration was considered incompatible with normal work operations but not considered escape impairing. Therefore, the 50 ppb (0.05 ppm) exposure from the Du Pont (1986) report is considered a protective POD for AEGL-2 derivation because the ocular irritation was neither escape impairing nor irreversible in humans. Although the 0.05 ppm exposure concentration is a protective POD for AEGL-2 derivation, it is assumed that the worker population upon which this is based was accustomed to the irritant effects of *n*-butyl isocyanate and that sensitive responders may experience similar effects at lower exposures. For these reasons an intraspecies uncertainty factor of 3 was applied for deriving the AEGL-2 values. Because *n*-butyl isocyanate is a contact irritant and because the ocular irritation is not dependent upon exposure duration, no time scaling was applied in the development of AEGL-2 values.

Proposed AEGL-3 values were based on a 4-hour $BMCL_{05}$ of 3.35 ppm from the Du Pont (1968) rat study. In the absence of an empirically derived exponent (*n*), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation. The 10-minute AEGL-3 value was set equivalent to the 30-minute value due to uncertainties in extrapolating from the 4-hour experimental value. Lethality data for *n*-butyl isocyanate are available for only one species and there is no information regarding lethality in humans. Therefore, an interspecies uncertainty factor of 10 is retained. Although the lethal response in rats exposed to *n*-butyl isocyanate exhibits latency, the initial insult appears to be the result of pulmonary damage. This mode of action is not likely to vary considerably across

individuals although dosimetric factors may be instrumental. To account for possible dosimetric variability, the intraspecies uncertainty factor is 3.

A motion was made by Dieter Heinz and seconded by John Hinz to accept AEGL-3 values as proposed. The motion passed (YES, 22; NO, 0; ABSTAIN: 0; Appendix G). A motion was then made by Dieter Heinz and seconded by John Hinz to accept AEGL-1 values as proposed, subject to validation of the human data from Du Pont. The motion passed (YES, 22; NO, 0; ABSTAIN: 0; Appendix G). Finally, a motion was made by Ernest Falke and seconded by Henry Anderson to accept AEGL-2 values as proposed, subject to validation of the human data from Du Pont. The motion passed (YES, 21; NO, 0; ABSTAIN: 1; Appendix G).

Summary of AEGL Values for *n*-butyl isocyanate (ppm)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	0.0017	0.0017	0.0017	0.0017	0.0017	0.-005 ppm lower range of ocular irritation (Du Pont, 1986); UF=3 (intrasp.); no time scaling
AEGL-2	0.017	0.017	0.017	0.017	0.017	0.05 ppm threshold for ocular irritation disallowing normal work but not impairing escape (Du Pont, 1986);); UF=3 (intrasp.); no time scaling
AEGL-3	0.22	0.22	0.18	0.11	0.057	4-hr $BMCL_{05}$ 3.35 ppm for lethality in rats (Du Pont, 1968); UF- 3 (intrasp.) and 10 (intersp.); n= 1or 3

Ethyl isocyanate (CAS No. 109-90-0)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Bob Young reviewed the data set for ethyl isocyanate (Attachment 8). Data are insufficient for derivation of AEGL-1 values for ethyl isocyanate. Therefore, AEGL-1 values were not recommended. In the absence of appropriate chemical-specific data, the proposed AEGL-3 values were divided by 3 to derive proposed AEGL-2 values for ethyl isocyanate. This approach is justified by the steep concentration-response curve (0% mortality in rats exposed to 27 ppm and 100% mortality at 82 ppm for 6-hr; Eastman Kodak, 1964). The concentration causing no deaths in rats (27 ppm for 6-hours; Eastman Kodak, 1964) was used as the point-of-departure for proposed AEGL-3 values. Death was observed at the next highest concentration tested (82 ppm for 6-hr). In the absence of an empirically derived exponent (*n*), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation. The 10-minute proposed AEGL-3 value was set equivalent to the 30-minute value due to uncertainties in extrapolating from the 6-hour experimental value (NRC, 2001). Lethality data for ethyl isocyanate are available for only one animal species and there is no information regarding

lethality in humans. Therefore, an interspecies uncertainty factor of 10 was retained. Clinical signs are consistent with contact irritation; this mode of action is not likely to vary considerably across individuals although dosimetric factors may vary. To account for possible dosimetric variability, the intraspecies uncertainty factor is 3. The intraspecies uncertainty factor of 3 is also supported by the steep concentration-response curve with regard to lethality (0% mortality in rats exposed to 27 ppm and 100% mortality at 82 ppm for 6-hr; Eastman Kodak, 1964), which implies limited intra-individual variability. A modifying factor of 3 was applied to account for the sparse database. Thus, the total proposed adjustment was 90.

After discussion, a motion was made by Richard Niemeier and seconded by John Hinz to adopt AEGL-3 values as proposed except that the modifying factor be increased from 3 to 10, resulting in an increase in overall adjustment from 90 to 300. The motion also included adopting AEGL-2 values by dividing the AEGL-3 values by 3 and not recommending AEGL-1 values. The motion passed (YES, 21; NO, 0; ABSTAIN: 1; Appendix H).

Summary of AEGL Values for ethyl isocyanate (ppm)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	Insufficient data
AEGL-2	0.070	0.070	0.053	0.033	0.023	One-third the AEGL-3 values
AEGL-3	0.21	0.21	0.16	0.10	0.068	Concentration causing no death in rats (27 ppm, 6-hr) (Eastman Kodak, 1964)

Phenyl isocyanate (CAS No. 103-71-9)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Bob Young reviewed the data set for phenyl isocyanate (Attachment 9). The proposed AEGL-1 values were based upon a 45-minute exposure of rats to 1.1 mg/m^3 (0.2 ppm). This exposure was considered to be a threshold for respiratory tract irritation (Pauluhn et al., 1995). In the total absence of human data and animal data available for only one species, the interspecies uncertainty factor of 10 was retained. Because phenyl isocyanate is a direct-contact irritant, the dynamic aspect of toxicity would not be expected to vary. It has been reported that isocyanates react with nucleophiles at the point of contact which, in respiratory tract tissue, includes proteins with sulfhydryl, hydroxyl, amine, and carboxyl groups. Pauluhn et al. (1995) noted that experimental evidence suggests that tissue damage is consistent with a persistent inflammatory response involving direct contact with the tissue. For this reason and because the POD appears to be a protective estimate (multiple exposures to higher concentrations produced no clinical signs or histopathologic evidence of pulmonary damage), the intraspecies uncertainty factor of 3 was considered sufficient. Because phenyl isocyanate is a contact irritant, its activity in this respect is not dependent upon exposure duration and no time scaling was considered necessary for the AEGL-specific exposure periods.

For proposed AEGL-2 derivation, the exposure of rats to 0.8 ppm was considered a no-effect level for AEGL-2 severity effects (Pauluhn et al., 1995). The interspecies uncertainty factor was 10 due to complete absence of human data and animal data in only one species. As for AEGL-1 derivation, the intraspecies uncertainty factor of 3 was used because phenyl isocyanate is a direct-contact irritant for which the dynamic aspect of toxicity would not be expected to vary. Pauluhn et al. (1995) noted that experimental evidence suggests that tissue damage is consistent with a persistent inflammatory response involving direct contact with the tissue. Furthermore, the critical effect and POD were from a multiple exposure study rather than a single acute exposure. The protective nature of the POD does not justify further uncertainty factor application. Because the critical effect is a likely a function of direct-contact irritation, no time scaling was considered necessary for the AEGL-specific exposure periods (NRC, 2001). Additionally, Pauluhn et al. (1995) clearly state that experimental evidence suggests that phenyl-isocyanate-induced respiratory tract damage is consistent with a persistent inflammatory response involving direct contact with tissues and that variability in response is a function of dosimetric variability rather exposure duration.

A toxicity bioassay in rats conducted by Bayer AG (1991a) served as the key study for proposed AEGL-3 development. The investigators commented that phenyl isocyanate exhibits a steep exposure-response relationship. In the absence of detailed exposure-response data suitable for quantitatively estimating a lethality threshold and consistent with AEGL methodologies (NRC, 2001), a lethality threshold of 1.5 ppm was estimated as a 3-fold reduction of the 4-hour LC_{50} of 4.6 ppm and served as the Point-of-Departure (POD) for AEGL-3 derivation. Uncertainty factors were applied and justified as described for AEGL-1 and AEGL-2 derivations. Although the initial injury to respiratory tract tissue following inhalation exposure to phenyl isocyanate is the result of direct-contact irritation, it is possible that exposure duration may be a component of irreversible injury that culminates in a lethality. Therefore, the AEGL-3 values were derived using a default time scaling (using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation). The default time scaling approach and subsequent adjustment by uncertainty factors results in an 8-hour AEGL-3 value of 0.025 ppm which is quite similar to the 8-hour AEGL-2 value. The 8-hour value time scaled directly from the animal data POD of 1.5 ppm results in an 8-hour value of 0.75 ppm. Bayer AG (1991b) reported that no rats died following exposure to 0.7 ppm for 6 hours per day for 5 days, implying that the default time scaling to 8 hours may be overly conservative (see Section 3.2.1). For this reason and for consistency with the 8-hour AEGL-2 value, the 4-hour AEGL-3 value was adopted as the 8-hour value. Due to uncertainties in extrapolating from the 4-hour POD to 10-minutes, the 30-minute value was adopted as the 10-minute value.

After significant discussion, a motion was made by Ernie Falke and seconded by John Hinz to adopt AEGL-3 values as proposed except that the interspecies UF be reduced from 10 to 3, resulting in a total UF of 10 (3 x 3). This approach should be supported with the repeated-exposure data showing that rats exposed to 2.1 ppm died only after multiple exposures; surviving rats fully recovered. Also, the resulting AEGL-3 values for phenyl isocyanate are supported by the toluene diisocyanate (TDI) values. The phenyl isocyanate AEGL-3 values are approximately 2-fold lower than the TDI values, and LC_{50} values are also 2-fold different. The motion passed (YES, 20; NO, 0; ABSTAIN: 0; Appendix I). A motion was then made by Ernest Falke and seconded by John Hinz to

adopt AEGL-2 values as proposed except that the interspecies UF be reduced from 10 to 3, resulting in a total UF of 10 (3 x 3). The motion passed (YES, 18; NO, 1; ABSTAIN: 1; Appendix I). Finally, a motion was made by Calvin Willhite and seconded by John Hinz to adopt AEGL-1 values as proposed except that the interspecies UF be reduced from 10 to 3, resulting in a total UF of 10 (3 x 3). The motion passed (YES, 20; NO, 0; ABSTAIN: 0; Appendix I).

Summary of AEGL Values for phenyl isocyanate						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	0.020 ppm	0.020 ppm	0.020 ppm	0.020 ppm	0.020 ppm	Exposure of rats to 0.2 ppm for 45 min.; threshold for respiratory tract irritation; UF=3x 3; no time scaling (Pauluhn et al., 1995)
AEGL-2	0.18 ppm	0.18 ppm	0.15 ppm	0.092 ppm	0.060 ppm	Multiple 6-hr exposures of rats to 0.8 ppm; exposure level was a no-effect level for AEGL-2 severity; UF=3x10; n=1 or 3 (Pauluhn et al., 1995)
AEGL-3	0.30 ppm	0.30 ppm	0.24 ppm	0.15 ppm	0.075 ppm	3-fold reduction of rat 4-hr LC_{50} (4.6 ppm/3=1.5 ppm) as an estimate of the lethality threshold; UF=3x10, n=1 or 3 (Bayer AG, 1991a)

Isobutyl isocyanate (CAS No. 1873-29-6)
t-Butyl isocyanate (CAS No. 1609-86-5)
n-Propyl isocyanate (CAS No. 110-78-1)
Isopropyl isocyanate (CAS No. 1795-48-8)
Methoxymethyl isocyanate (CAS No. 6427-21-0)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Bob Young discussed deriving AEGL values for isobutyl isocyanate, t-butyl isocyanate, n-propyl isocyanate, isopropyl isocyanate, and methoxymethyl isocyanate by analogy to n-butyl isocyanate. This discussion was post-poned to NAC-46 (June, 2008) to determine if more chemical structure-activity data could be obtained.

Methyl Isothiocyanate (CAS No. 556-61-6)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Sylvia Talmage discussed the toxicity data for methyl isothiocyanate (Attachment 10). The isothiocyanates are considerably less toxic than the isocyanates. Adequate summaries of acute and repeat inhalation exposure studies with the rat were available from secondary sources. Methyl isothiocyanate is a potent, direct-acting irritant. The AEGL-1 was based on a well-conducted clinical study with 70 individuals. A suggested NOEL of 0.22 ppm for eye irritation, the most sensitive endpoint in several studies, was raised to 0.80 ppm. The 0.80 ppm was a LOEL for eye irritation in the clinical study, but was considered a NOAEL for eye irritation according to the definition of the AEGL-1 (no blinking or redness). An intraspecies uncertainty factor of unity was considered appropriate for a no-effect concentration for this sensitive endpoint. As the 0.80 ppm NOAEL was tested for up to 4 hours, this same value was used for all AEGL-1 exposure durations. It was moved by Marcel van Raaij and seconded by Richard Niemeier to accept the 0.80 ppm value across all exposure durations. The motion passed (YES: 17; NO: 0; ABSTAIN: 0; Appendix J).

As no data relevant to the definition of an AEGL-2 were available, and in light of the steep concentration-response curve for methyl isothiocyanate, the AEGL-2 values were derived by dividing the AEGL-3 values by 3. The points of departure for the AEGL-3 were the 1-hour and 4-hour highest non-lethal concentrations of 210 and 80 ppm, respectively, in studies with the rat (Clark and Jackson 1977; Jackson et al. 1981). Application of interspecies and intraspecies uncertainty factors of 3 each for a total of 10, generally applied to chemicals for which the mode of action is that of a direct-acting irritant (NRC 2001), resulted in values inconsistent with well-conducted repeat-exposure studies in rats. Therefore, interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were applied. The 1-hour value of 210 ppm was used to derive the 10- and 30-minute and 1-hour AEGL-3 values; the 4-hour concentration of 80 ppm was used to derive the 4- and 8-hour values. Time-scaling used the default values of $n = 3$ and $n = 1$ for shorter and longer exposure durations, respectively (NRC 2001). It was moved by Ernest Falke and seconded by George Woodall to accept the AEGL-3 values. The motion passed (YES: 18; NO; 0; ABSTAIN: 0; Appendix J). It was then moved by Richard Niemeier and seconded by David Freshwater to derive the AEGL-2 values by dividing the AEGL-3 values by 3. The motion passed (YES: 17; NO: 0; ABSTAIN: 0; Appendix J).

Summary of AEGL Values for Methyl Isothiocyanate						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL–1	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	NOAEL for eye irritation at several time points – humans (Russell and Rush 1996)
AEGL–2	43 ppm (130 mg/m^3)	29 ppm (87 mg/m^3)	23 ppm (69 mg/m^3)	9.0 ppm (27 mg/m^3)	4.3 ppm (13 mg/m^3)	AEGL-3 values divided by 3; steep concentration-response curve for lethality (NRC 2001)
AEGL–3	130 ppm (390 mg/m^3)	88 ppm (260 mg/m^3)	70 ppm (210 mg/m^3)	27 ppm (81 mg/m^3)	13 ppm (39 mg/m^3)	1- and 4-hour highest non-lethal concentrations – rat (Clark and Jackson 1977; Jackson et al. 1981)

Ethyl Phosphorodichloridate (CAS No. 1498-51-7)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Gail Chapman, U.S. Navy

Cheryl Bast presented an overview of relevant data and development of the draft AEGL values (Attachment 11). Data were insufficient for derivation of AEGL-1 values. Therefore, AEGL-1 values were not recommended for ethyl phosphorodichloridate. In the absence of appropriate chemical-specific data, a fractional reduction of the AEGL-3 values may be used to derive AEGL-2 values (NRC, 2001). The proposed AEGL-3 values were divided by 10 to derive proposed AEGL-2 values for ethyl phosphorodichloridate. In cases of a steep-concentration-response curve, AEGL-3 values may be divided by 3 to estimate AEGL-2 values (NRC, 2001). However, rat lethality data for ethyl phosphorodichloridate suggest that the concentration-response curve is not steep (4-hour exposure: 0% mortality at 37 ppm, 20% mortality at 61 ppm; 20% mortality at 75 ppm; 60% mortality at 90 ppm; 85% mortality at 143 ppm,; and 100% mortality at 355 ppm; Bayer, 1983). Therefore, the factor of 3 is not considered sufficient, and proposed AEGL-2 values were estimated by dividing proposed AEGL-3 values by 10. A combined male and female rat 4-hour $BMCL_{05}$ of 38.0 ppm (Bayer, 1983) was used as the point-of departure (POD) for proposed AEGL-3 values. This is considered a threshold for lethality, and is supported by the fact that no mortality was observed in this study in rats exposed to 37 ppm for 4 hours. Values were scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-minute value was adopted as the 10-minute value due to the added uncertainty of extrapolating from the 4-hour POD to the 10-minute AEGL-3 value. Inter- and intra-species uncertainty factors of 3 each were applied (total UF = 10). Ethyl phosphorodichloridate appears to be a primary contact irritant.

Rat studies suggest that vapors are irritating to the eyes and nose, and that pulmonary edema increases as concentration increases (Rhone Poulenc, Inc., 1990; Bayer, 1983). The liquid was corrosive to the skin and eyes of rabbits (Rhone Poulenc, Inc., 1990). It also reportedly reacts with water to produce hydrogen chloride, which supports a mechanism of primary irritation. These types of portal of entry effects are not expected to vary greatly within or between species. Therefore, the total UF of 10 was considered sufficient. After discussion, a motion was made by Dieter Heinz and seconded by Marcel van Raaij to accept AEGL-3 values as presented except that the 10-minute AEGL-3 value be derived by time scaling. Even though the POD was 4-hours, the time scaling approach is supported by the Bayer (1983) saturated vapor experiment showing no mortality in rats exposed to approximately 20,000 ppm for 10-minutes. The motion passed (YES, 18; NO, 0; ABSTAIN: 2; Appendix K). A motion was then made by Ernie Falke and seconded by George Woodall to derive AEGL-2 values by dividing the AEGL-3 values by 10 and to adopt NR for AEGL-1 values. The motion passed (AEGL-2: YES, 19; NO, 0; ABSTAIN: 1; Appendix K). (AEGL-1: YES, 20; NO, 0; ABSTAIN: 0; Appendix K)

Summary of AEGL Values for Ethyl phosphorodichloridate						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1	NR	NR	NR	NR	NR	-
AEGL-2	1.1 ppm 7.3 mg/m^3	0.76 ppm 5.0 mg/m^3	0.60 ppm 4.0 mg/m^3	0.38 ppm 2.5 mg/m^3	0.19 ppm 1.3 mg/m^3	One-tenth the AEGL-3 Values
AEGL-3	11 ppm 73 mg/m^3	7.6 ppm 50 mg/m^3	6.0 ppm 40 mg/m^3	3.8 ppm 25 mg/m^3	1.9 ppm 13 mg/m^3	Four-hour threshold for lethality ($BMCL_{05}$) in rats (Bayer, 1983)

1,2-Butylene Oxide (CAS No. 106-88-7)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Jim Holler, ATSDR

Sylvia Talmage discussed the toxicity data for 1,2-butylene oxide (Attachment 12). Acute, repeat-exposure, and chronic toxicity/carcinogenicity studies were available for the mouse and rat. 1,2-Butylene oxide is a direct-acting irritant. The AEGL-1 was based on a NOAEL for eye irritation of 721 ppm in rats during a 4-hour exposure (NTP 1988). The value was supported by a 7-hour exposure of rats to 1000 ppm, during which respiratory rate was moderately depressed (Reitz et al. 1983). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied as slight irritation is not expected to differ greatly between species or among humans. The same value was used across all exposure durations because the exposure was 4 hours and there is adaptation to the slight irritation that defines the AEGL-1.

The point of departure for the AEGL-2 was the 4-hour exposure of rats to 1420 ppm during which eye irritation was seen (NTP 1988). Interspecies and intraspecies uncertainty factors of 3 each for a

total of 10 were applied because the mechanism of action is direct irritation which is not expected to differ greatly between species or among humans. The same value was used across all exposure durations because the exposure was for 4 hours.

The point of departure for the AEGL-3 was the 4-hour exposure of rats to the highest non-lethal concentration, 2050 ppm (NTP 1988). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied because the mechanism of action is direct contact irritation, resulting in respiratory tract congestion and hemorrhage, which is not expected to differ greatly between species or among humans. Time-scaling ($C^n \times t = k$) used n values of 3 and 1 for shorter and longer exposure durations, respectively. The 10-minute value was set equal to the 30-minute values because of the uncertainty in time-scaling from 4 hours to 10 minutes. The 8-hour AEGL-3 value was set equal to the 4-hour value based on lack of serious effects in rats and mice in repeat exposures studies at concentrations of 150 and 400 ppm. It was moved by John Hinz and seconded by Dieter Heinz to accept the proposed AEGL values (voted on separately). The motions passed: (YES: 19; NO: 0; ABSTAIN: 0; Appendix L).

A short discussion centered on the increased sensitivity of the mouse to lethal concentrations of 1,2-butylene oxide compared with the rat. It was suggested that a discussion of the increased sensitivity of the mouse to glutathione depletion (the mode of metabolism/detoxification for 1,2-butylene oxide) compared with the rat be added to the technical support document. Interim AEGL values for the related chemical, propylene oxide, will be added to the technical support document. The LOA for 1,2-butylene oxide, derived by Roberta Grant, will also be added to the document. Bob Benson is doing the cancer assessment for 1,2-butylene oxide. Following addition of all of these sections, the technical support document will be circulated to NAC members.

Summary of AEGL Values for 1,2-Butylene Oxide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	72 ppm	72 ppm	72 ppm	72 ppm	72 ppm	NOAEL for eye irritation, 4 hours – rat (NTP 1988)
AEGL–2	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm	Eye irritation, 4 hours – rat (NTP 1988)
AEGL–3	410 ppm	410 ppm	330 ppm	210 ppm	210 ppm	4-Hour highest non-lethal concentration – rat (NTP 1988)

SPECIAL PRESENTATION

BENCHMARK:

Dr. Jay Zhao (U.S. EPA) presented an overview of the benchmark concentration software (Attachment 13) and dose-response modeling techniques for AEGL derivation.

GENERAL ISSUES

ADMINISTRATIVE MATTERS

There was one response to the request for NAC member volunteers to present and defend TSDs to the COT subcommittee. Bob Benson will present the vinyl chloride TSD.

The next meeting of the NAC/AEGL will be held June 25-27, 2008, in Boston, MA.

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast, Sylvia Talmage, and Robert Young, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

Attachment 1. Meeting 45 agenda
Attachment 2. Meeting 45 attendee list
Attachment 3. 1,1,1-Trichloroethane presentation
Attachment 4. Nitrogen oxides presentation
Attachment 5. Ethyl benzene presentation
Attachment 6. Cyanogen presentation
Attachment 7. n-Butyl isocyanate presentation
Attachment 8. Ethyl isocyanate presentation
Attachment 9. Phenyl isocyanate presentation
Attachment 10. Methyl isothiocyanate presentation
Attachment 11. Ethyl phosphorodichloridate presentation
Attachment 12. 1,2-Butylene oxidepresentation
Attachment 13. Benchmark Dose Presentation
Attachment 14. Meeting certification by Chair

LIST OF APPENDICES

Appendix A. Ballot for NAC-44 meeting summary
Appendix B. Final NAC-44 Meeting Highlights
Appendix C. Ballot for nitrogen tetroxide
Appendix D. Ballot for nitrogen trioxide
Appendix E. Ballot for ethyl benzene
Appendix F. Ballot for cyanogen
Appendix G. Ballot for n-butylisocyanate
Appendix H. Ballot for ethyl isocyanate
Appendix I. Ballot for phenyl isocyanate
Appendix J. Ballot for methyl isothiocyanate
Appendix K. Ballot for ethyl phosphorodichloridate
Appendix L. Ballot for 1,2-butylene oxide