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

June 25-27, 2008

Meeting-46 Highlights

Boston Radisson
200 Stuart Street
Boston, MA

INTRODUCTION

Ernie Falke discussed the chemical scheduling for the next AEGL meeting (December, 2008). George Rusch requested that if people would like chemicals to be added to the chemical list, they should communicate their requests to the NAC. Richard Neimeier will share the Homeland security chemical list if possible; it is sensitive information.

The draft NAC/AEGL-45 meeting highlights were reviewed. George Woodall pointed out that the AEGL-2 time scaling for phenyl isocyanate required correction. A motion was made by John Hinz and seconded by Henry Anderson to accept the minutes as proposed with the aforementioned correction. The motion passed unanimously by a show of hands (Appendix A). The Final NAC/AEGL-45 meeting highlights are attached (Appendix B).

The highlights of the NAC/AEGL-46 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-46 Agenda.

FEDERAL REGISTER 11

Sixty-two chemicals were included in the FR11 publication. The 61 chemicals not receiving comments are elevated to interim status. Chemicals elevated to interim status include: 1,2-Dibromoethane (106-93-4), 2-Ethylhexyl chloroformate (24468-13-1), Allyl chloride (107-05-1), Allyl chloroformate (2937-50-0), Allyl trichlorosilane (107-37-9), Amyl trichlorosilane (107-72-2), Benzyl chloroformate (501-53-1), Boron tribromide (10294-33-4), Bromine chloride (13863-41-7), Butyl trichlorosilane (7521-80-4), BZ (3-Quinuclidinyl benzilate) (6581-06-2), Carbonyl fluoride (353-50-4), Carbonyl sulfide (463-58-1), Chlorobenzene (108-90-7), Chloromethyltrichlorosilane (1558-25-4), Chloropicrin (76-06-2), Chlorosulfonic acid (7790-94-5), Chlorotrifluoroethylene (79-

38-9), Dichlorosilane (4109-96-0), Diethyldichlorosilane (1719-53-5), Diketene (674-82-8), Dimethylamine (124-40-3), Dimethylchlorosilane (1066-35-9), Diphenyldichlorosilane (80-10-4), Docecytrichlorosilane (4484-72-4), Ethylamine (75-04-7), Ethyl chloroformate (541-41-3), Ethyl chlorothioformate (2941-64-2), Ethylene chlorohydrin (107-07-3), Ethyltrichlorosilane (115-21-9), Hexyltrichlorosilane (928-65-4), Isobutyl chloroformate (543-27-1), Isopropyl chloroformate (108-23-6), Methacrylaldehyde (78-85-3), Methanesulfonyl chloride (124-63-0), Methyl amine (74-89-5), Methyl chloroformate (79-22-1), Methyl vinyl ketone (78-94-4), Methylvinyl dichlorosilane (124-70-9), n-Butyl chloroformate (592-34-7), Nonyltrichlorosilane (5283-67-0), Octadecyl trichlorosilane (112-04-9), Octyltrichlorosilane (5283-66-9), Osmium tetroxide (20816-12-0), Oxygen difluoride (7783-41-7), Pentaborane (19624-22-7), Phenyl chloroformate (1885-14-9), Propyl chloroformate (109-61-5), Propyltrichlorosilane (141-57-1), sec-Butyl chloroformate (17462-58-7), Silicon tetrachloride (10026-04-7), Silicon tetrafluoride (7783-61-1), Stibine (antimony hydride) (7803-52-3), Sulfuryl fluoride (2699-79-8), Tetrafluoroethylene (116-14-3), Thionyl chloride (7719-09-7), Trichloro(dichlorophenyl)silane (27137-85-5), Trichlorophenylsilane (98-13-5), Trichlorosilane (10025-78-2), Trimethylamine (75-50-3), Vinyl trichlorosilane (75-94-5).

Comments were received for acrylonitrile (107-13-1). These comments will be addressed at NAC-47 (December, 2008).

NO DATA CHEMICALS

3,5-Dichloro-2,4,6-trifluoropyridine (CAS No. 1737-93-5)
Acetyl chloride (CAS No. 75-36-5)
Arsenic pentaoxide (CAS No. 1303-28-2)
Ethylphosphonous dichloride (CAS No. 1498-40-4)
Methyl paroxon (CAS No. 950-35-6)
Nitrosyl chloride (CAS No. 2696-92-6)
Sodium dithionite (CAS No. 7775-14-6)
Trifluoroacetyl chloride (CAS No. 354-32-5)

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

Staff Scientists: Cheryl Bast, ORNL; Robert Young, ORNL
Chemical Manager: Ernest Falke, U.S. EPA; Susan Ripple, Dow Chemical

There are no data currently available for development of AEGL values for 3,5-Dichloro-2,4,6-trifluoropyridine; Acetyl chloride; Arsenic pentaoxide; Ethylphosphonous dichloride; Methyl paroxon; Nitrosyl chloride; Sodium dithionite; Trifluoroacetyl chloride; Isobutyl isocyanate; Isopropyl isocyanate; Methoxymethyl isocyanate; n-Propyl isocyanate; t-Butyl isocyanate. George Rusch suggested contacting the organizations that nominated these chemicals to inform them that data are needed to derive AEGL values. Paul Tobin will follow up on this suggestion. If no data become available, these chemicals will be placed in holding status. Marcel VanRaaij suggested deriving AEGL values for arsenic pentoxide by analogy to arsenic; this suggestion will be evaluated for NAC-47.

CHEMICAL REVISITS/STATUS UPDATES

Phosgene (CAS No. 75-44-5)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA

Cheryl Bast reviewed recently published phosgene data (Attachment 3). New studies consist of an acute rat lethality study, a rat lung parameter study, and an acute dog study. The phosgene TSD is final status and is published in Volume 2. Potential AEGL values calculated with the new studies were compared with the published AEGL values and discussion was focused on whether to revise the AEGL values for phosgene and prepare a new TSD. A motion was made by John Hinz and seconded by Dieter Heinz not to reconsider AEGL values for phosgene at this time because values calculated with the recently published data are not expected to be meaningfully different. The values may be reconsidered when an SOP guidance for revisiting finalized AEGL values becomes available. The motion passed by a show of hands (YES: 18; NO: 1; ABSTAIN: 0; Appendix C). Richard Neimeier stated that WHO searches literature every 7 years; if new data are available the chemical is revisited. George Woodall stated that the IRIS program revisits chemicals every 10 years and may expedite a review when necessary. Jim Holler stated that ATSDR re-evaluated potential new data every 3 years. Criteria for AEGL document revisits will be presented to the NAC committee at a future meeting and will be included as an SOP amendment.

Methyl Iodide (CAS No. 74-88-4)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Alan Becker, Missouri

This chemical was deferred until NAC-47 (December, 2008) for PBPK modeling. Dr. Beth Mileson (Arysta Life Sciences) attended the meeting and will run a PBPK model developed by Lisa Sweeney for AEGL-2 (endpoint is 100 ppm for 6-hr). There was a short discussion regarding not using rabbit fetotoxicity data as an endpoint. Sylvia explained that the rabbit placenta does not regulate iodine uptake; whereas, the human and rat placentas do regulate iodine uptake. Therefore, the rabbit is not an appropriate species to extrapolate to the human.

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

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bob Benson, U.S. EPA

This chemical was deferred until NAC-47 (December, 2008) for PBPK modeling.

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

Staff Scientist: Carol Wood, ORNL
Chemical Manager: John Hinz, U.S. Air Force

Chemical manager John Hinz presented a brief review of the history of this TSD and Carol Wood discussed the derivation of the AEGL-2 values (AEGL-1 and AEGL-3 values were balloted at previous meetings) (Attachment 4). Proposed AEGL-2 values (2900 ppm for 10-min, 1600 ppm for 30-min, 1100 ppm for 1-hr, 660 ppm for 4-hr, and 580 ppm for 8-hr) were derived using PBPK modeling run with a CNS endpoint (minimum narcotic concentration) of 1500 ppm for 4-hr (Molnar et al., 1986). An interspecies UF of 1 was applied and is considered sufficient with the PBPK modeling approach because similar CNS effects occur in humans and animals. An intraspecies UF of 3 was applied because the minimum alveolar concentration for volatile anesthetics does not vary by more than a factor of 2- to 3-fold among humans. There was significant discussion regarding the ototoxicity noted in repeated-exposure studies in rats. A motion was made by Bob Benson and seconded by Marcel vanRaaij to accept AEGL-2 values as proposed with the caveat that the document has a statement indicating that the values may not protect for ototoxicity. In addition, discussion should be added suggesting that the AUC (and not the Cmax currently used in the PBPK model) is likely responsible for ototoxicity. Discussion about observations in other hydrocarbons and acknowledgment that no acute data for ototoxicity in ethyl benzene are available should be included in the TSD. The motion passed (YES: 19; NO: 0; ABSTAIN: 1; Appendix D).

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	**2900 ppm**	**1600 ppm**	**1100 ppm**	**660 ppm**	**580 ppm**	**Minimum narcotic concentration in rats (Molnar et al., 1986)**
AEGL-3	4700 ppm	2600 ppm	1800 ppm	1000 ppm	910 ppm	Highest non-lethal concentration in rats (Andersson et al., 1981)

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

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

Bob Young explained that although n-butyl isocyanate values were previously balloted at NAC-45 (March, 2008), recent information provided via Haskell Laboratories indicates that determination of n-butyl isocyanate in the occupational settings underestimated the exposure levels in the key reports (DuPont, 1986) (Attachment 5). The findings were based upon a comparison of the older impinger/GC method vs a more recent XAD7/HPLC method. The XAD7/HPLC method gave results that were 40% higher than the older method. At air levels <20 ppb, the newer method gave values 2 to 4 times higher than the older impinger/GC method. Therefore, proposed AEGL values for n-butyl isocyanate have been adjusted based on these findings (proposed AEGL-1 value of 0.0068 ppm at all time points; proposed AEGL-2 value of 0.024 ppm at all time points; proposed AEGL-3 values of 0.31 ppm for 10- and 30-min, 0.25 ppm for 1-hr, 0.15 ppm for 4-hr, and 0.080 ppm for 8-hr). The differences between the original AEGL values and the newly proposed adjusted values are slight (approx. 1.5 to 4-fold). After extensive discussion, a motion was made by Marcel vanRaaij and seconded by John Hinz to accept AEGL-1 values of 0.013 ppm at all time points, AEGL-2 values of 0.023 ppm at all time points, and AEGL-3 values as proposed. The AEGL-1 is based on a POD of 0.040 ppm (the middle of the no ocular irritation range from two DuPont IH surveys); an intraspecies uncertainty factor of 3 was applied (contact irritation). The AEGL-2 is based on a POD of 0.05 ppm (ocular irritation noted, normal work operations were not possible, but escape was not impaired). The 0.05 ppm POD was multiplied by 1.4 (increase of 40%) to account for the analytical underestimations described in the recently acquired DuPont data. An intraspecies UF of 3 was applied (contact irritation). The AEGL-3 values were based on a 4-hour $BMCL_{05}$ in rats of 3.35 ppm; This POD was multiplied by 1.4 (increase of 40%) to account for the analytical underestimations described in the recently acquired DuPont data. The motion passed (YES: 19; NO: 0; ABSTAIN: 0; Appendix E).

Summary of AEGL Values for *n*-butyl isocyanate (ppm)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**

AEGL-1	0.013	0.013	0.013	0.013	0.013	0.04 ppm NOEL for ocular irritation (Du Pont, 1986); UF=3 (intrasp.); no time scaling
AEGL-2	0.023	0.023	0.023	0.023	0.023	0.05 ppm threshold for ocular irritation disallowing normal work but not impairing escape (Du Pont, 1986); adjusted by 1.4 for analytical method; UF=3 (intrasp.); no time scaling
AEGL-3	0.31	0.31	0.25	0.15	0.080	4-hr $BMCL_{05}$ 3.35 ppm for lethality in rats (Du Pont, 1968); adjusted by 1.4 for analytical method; UF- 3 (intrasp.) and 10 (intersp.); n= 1or 3

REVIEW of PRIORITY CHEMICALS

Trimethylacetyl chloride (CAS No. 3282-30-2)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rusch, Honeywell

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for trimethylacetyl chloride (Attachment 6). AEGL-1 values were not recommended due to insufficient data. Proposed AEGL-2 values (2.0, 2.0, 1.6, 1.0, and 0.67 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 (5.9, 5.9, 4.7, 3.0, and 2.0 ppm for the 10-min., 30-min., 1-hr, 4-hr, and 8-hr durations, respectively), were based on the concentration causing no deat in rats (78 ppm for 6-hr) (Eastman Kodak, 1992). Intraspecies and interspecies uncertainty factors of 3 each were proposed because contact irritation/portal of entry effects are not expected to vary widely within or between species. A modifying factor of 3 was proposed due to the sparse data base. Data for deriving a chemical-specific time-scaling exponent were not available; therefore, default time scaling was proposed (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). After a short discussion, a motion was made by John Hinz and seconded by Dieter Heinz to adopt AEGL values as proposed except that the interspecies UF be increased from 3 to 10 because data from a mouse RD_{50} study suggested that mice are more sensitive than rats. The motion passed (YES: 21; NO: 0; ABSTAIN: 0; Appendix F). Information comparing the values with phosgene AEGLs will be added to the TSD to make the point that this chemical may be reaching the deep lung and values forthis chemical and phosgene are consistent with one another.

Summary of AEGL Values for Trimethylacetyl chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Insufficient data
AEGL–2	0.67 ppm	0.67 ppm	0.53 ppm	0.33 ppm	0.22 ppm	One third the AEGL-3 values (NRC, 2001)
AEGL–3	2.0 ppm	2.0 ppm	1.6 ppm	0.99 ppm	0.65 ppm	6-hour exposure causing no mortality in the rat (Eastman Kodak, 1992). Inter UF = 10; Intra UF =3; MF = 3. n= 1 or 3

Germane (CAS No. 7782-65-2)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: David Freshwater, U.S. DOE

Cheryl Bast reviewed the limited data set for germane (Attachment 7). Data were insufficient to derive AEGL-1 values for germane. Therefore, proposed AEGL-1 values were not recommended. Chemical-specific data are insufficient for derivation of AEGL-2 or AEGL-3 values for germane. However, Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine for 2 hours exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure. A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. Therefore, the AEGL-2 values for arsine were proposed as AEGL-2 values for germane, and the AEGL-3 values for arsine were proposed as AEGL-3 values for germane. After discussion, a motion was made by Richard Niemeier and seconded by Bob Benson to accept the AEGL values as proposed. The motion passed (YES: 19; NO: 0; ABSTAIN: 2; Appendix G). The TSD will be revised to better define the mode of action (hemolysis) and explain why values were derived by analogy to arsine and not stibine (also a hemolytic).

Summary of AEGL Values for Germane						
Classification	**10-mim**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data

AEGL-2 (Disabling)	0.30 ppm	0.21 ppm	0.17 ppm	0.040 ppm	0.020 ppm	Arsine AEGL-2 values adopted as Germane AEGL-2 values (NRC, 2000; NRC, 2007)
AEGL-3 (Lethal)	0.91 ppm	0.63 ppm	0.50 ppm	0.13 ppm	0.060 ppm	Arsine AEGL-3 values adopted as Germane AEGL-3 values (NRC, 2000; NRC, 2007)

Methyl parathion (CAS No. 298-00-0)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Jim Holler, ATSDR

Bob Young reviewed the data set for methyl parathion (Attachment 8). AEGL-1 values were not recommended due to insufficient data. Proposed AEGL-2 values (1.5 mg/m^3 for 10-and 30-min, , 1.2 mg/m^3 for 1-hr, 0.73 mg/m^3 for 4-hr, and 0.37 mg/m^3 for 8-hr) were derived by dividing the AEGL-3 values by 3; this approach was supported by the steep concentration-response curve. Proposed AEGL-3 values (4.4 mg/m^3 for 10-and 30-min, , 3.5 mg/m^3 for 1-hr, 2.2 mg/m^3 for 4-hr, and 1.1 mg/m^3 for 8-hr) were based on a 4-hr rat $BMCL_{05}$ of 66.6 mg/m^3 (U.S. EPA, 1998). An interspecies UF of 3 was applied because variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present, and humans have greater levels of plasma cholinesterase than other species. An intraspecies UF of 10 was applied because of the documented variability in sensitivity between genders among different age groups, and the known genetic polymorphisms in A-esterases. Data for deriving a chemical-specific time-scaling exponent were not available; therefore, default time scaling was proposed (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 30-min AEGL-3 value was proposed as the 10-min value because the POD is 4-hr. After discussion, a motion was made by Gail Chapman and seconded by Bob Benson to adopt AEGL values as proposed except to time scale the 10-min value. This approach is justified because the concentration-response for cholinesterase follows a linear path. The motion passed (YES: 20; NO: 0; ABSTAIN: 0; Appendix H). The Thyssen (1979) study will be used to support AEGL-2 values.

Summary of AEGL Values for Methyl parathion						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL-2 (Disabling)	2.1 mg/m^3	1.5 mg/m^3	1.2 mg/m^3	0.73 mg/m^3	0.37 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; U.S. EPA, 1998)
AEGL-3	6.4 mg/m^3	4.4 mg/m^3	3.5 mg/m^3	2.2 mg/m^3	1.1 mg/m^3	Derived based upon a 4-hr

(Lethality)						$BMCL_{05}$ of 66.6 mg/m^3 for lethality in rats (U.S. EPA, 1998); UF = 3 (intersp.) and 10 (intrasp.); n = 1or 3

Parathion (CAS No. 56-38-2)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Jim Holler, ATSDR

Bob Young reviewed the data set for parathion (Attachment 9). Data are insufficient for derivation of AEGL-1 values for parathion. Therefore, AEGL-1 values were not recommended. AEGL-2 and AEGL-3 values were based on a 4-hr rat study from Edgewood Arsenal using 99.3% parathion. A BMC_{01} for tremors (28.9 mg/m^3) was used as the POD for AEGL-2 values. The presence or absence of tremors was considered discontinuous, quantal data and appropriate for BMC analysis; convulsion data were discounted as a POD for AEGL-2 values because of closeness to the lethality threshold. The BMC calculations were performed without including the top experimental concentration (230.5 mg/m^3), because use of all data points yielded a low p value (p=0.0002). Analysis of residuals by the Benchmark Dose program indicated this data point to be obstructive in the calculation of BMC values. Exclusion of the 230.5 mg/m^3 data point resulted in a much improved p-value (p= 0.5741). There were discussions in favor or against exclusion of this data point. One argument is that the exclusion can be justified by the EPA guidance on BMD calculations. In addition, the calculations are focused on the low region of the dose response curve so the deletion of that top dose would not make a considerable difference. Others indicated that the three top concentrations could be deleted because the response was reaching a plateau and the analysis should focus on the linear region of the lethal responses. AEGL-3 values were based on a BMC_{01} for lethality (37.5 mg/m^3).

For both AEGL-2 and AEGL-3 values, an interspecies UF of 3 was applied because variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present, and humans have greater levels of plasma cholinesterase than other species. An intraspecies UF of 10 was applied because of the documented variability in sensitivity between genders and among different age groups, and the known genetic polymorphisms in A-esterases. Data for deriving a chemical-specific time-scaling exponent were not available; therefore, default time scaling was proposed (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). Time- scaling was used for the 10-min because the concentration-response for cholinesterase follows a linear path. For AEGL-1 and AEGL-3 values, the motion was made by John Hinz and seconded by Jim Holler; the motion passed (YES: 20; NO: 0; ABSTAIN: 1; Appendix I). The motion for AEGL-2 values was made by Bob Benson and seconded by Calvin Willhite; this motion passed (YES: 16; NO: 1; ABSTAIN: 4; Appendix I).

Summary of AEGL Values for Parathion						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL-2 (Disabling)	2.8 mg/m^3	1.9 mg/m^3	1.5 mg/m^3	0.96 mg/m^3	0.48 mg/m^3	Derived based upon a 4-hr BMC_{01} of 28.9 mg/m^3 for tremors in rats (Edgewood Arsenal); UF = 3 (intersp.) and 10 (intrasp.); n = 1or 3
AEGL-3 (Lethality)	3.6 mg/m^3	2.5 mg/m^3	2.0 mg/m^3	1.3 mg/m^3	0.63 mg/m^3	Derived based upon a 4-hr BMC_{01} of 37.5 mg/m^3 for lethality in rats (Edgewood Arsenal); UF = 3 (intersp.) and 10 (intrasp.); n = 1or 3

Phorate (CAS No. 298-02-2)

Staff Scientist: Tom Marshall, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Sylvia Talmage reviewed the data set for phorate on behalf of Tom Marshall (Attachment 10). AEGL-1 values were not proposed due to insufficient data. Proposed AEGL-2 values (0.073 mg/m^3 for 10-min, 0.050 mg/m^3 for 30-min, 0.040 mg/m^3 for 1-hr, 0.010 mg/m^3 for 4-hr, and 0.0050 mg/m^3 for 8-hr) were derived by dividing the AEGL-3 values by 3; this approach was supported by the steep concentration-response curve. Proposed AEGL-3 values (0.22 mg/m^3 for 10-min, 0.15 mg/m^3 for 30-min, 0.12 mg/m^3 for 1-hr, 0.031 mg/m^3 for 4-hr, and 0.015 mg/m^3 for 8-hr) were based on a POD of 3.67 mg/m^3 (one-third of the 1-hr LC_{50} value for female rats; estimated non-lethal concentration) (Newell and Dilley, 1978). An interspecies UF of 3 was applied because variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present, and humans have greater levels of plasma cholinesterase than other species. An intraspecies UF of 10 was applied because of the documented variability in sensitivity between genders and among different age groups, and the known genetic polymorphisms in A-esterases. Data for deriving a chemical-specific time-scaling exponent were not available; therefore, default time scaling was proposed (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). A motion was made by Bob Benson and seconded by John Hinz to accept AEGL values as proposed. The motion passed (YES: 20; NO: 0; ABSTAIN: 0; Appendix J). The revised TSD will include a section on dermal/percutaneous data. Paul Tobin will contact EPA/OPP to obtain feedback on the AEGL values for the organophosphates.

Summary of AEGL Values for Phorate						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**

AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL-2 (Disabling)	0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; U.S. EPA, 1998)
AEGL-3 (Lethality)	0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3	Derived based upon an estimated 1-hr threshold for lethality in female rats of 3.67 mg/m^3 (one-third the LC_{50}); (Newell and Dilley, 1978); UF = 3 (intersp.) and 10 (intrasp.); n = 1or 3

tert-Octyl mercaptan (CAS No. 141-59-3)

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

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 tert-octyl mercaptan. In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to derive proposed AEGL-2 values for tert-octyl mercaptan. This approach is justified by the steep concentration-response curve. [A 4-hour exposure to 38 ppm caused 0% lethality in male rats and 100% mortality was noted at 64 ppm (Fairchild and Stokinger, 1958); a 4-hour exposure to 59 ppm caused 0% lethality in male rats and 80% lethality was noted at 71 ppm, and a 12 ppm exposure caused 10% lethality in female rats, whereas, 100% mortality was noted at 18 ppm (Atochem, 1982). Also, male rats exposed to 73 ppm for 4-hours showed 0% mortality and 100% mortality was noted at 79 ppm (Amoco, 1979). In mice exposed for 4-hours, 0% mortality was noted at 38 ppm and 100% mortality at 64 ppm (Fairchild and Stokinger, 1958).] A 4-hour $BMCL_{05}$ value of 11.5 ppm calculated from combined female rat data (Atochem, 1982) was used as the point-of-departure (POD) for proposed AEGL-3 values. This is considered a threshold for lethality calculated from the most sensitive test animals (females). This POD was chosen over the most conservative benchmark value calculated from a single study (10.1 ppm) because the statistical goodness-of fit was much greater from the combined data set ($p = 0.86$ for combined data set, whereas, $p = 0.15$ for single female data set presented in Table 4). An intraspecies uncertainty factor of 3 was applied and is considered sufficient because the POD is from the more sensitive female animals. Also, the steep concentration-response curve implies limited individual variability. An interspecies uncertainty factor of 3 was also applied because the limited data suggest no difference in species sensitivity between rats and mice. 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. The 30-minute AEGL-3 value was adopted as the 10-

minute value due to the uncertainty in extrapolating from the 4-hour POD. A motion was made by Richard Niemeier and seconded by George Woodall to accept the AEGL values as proposed. The motion passed (YES: 18; NO: 0; ABSTAIN: 0; Appendix K).

Summary of AEGL Values for tert-octyl Mercaptan						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	0.77 ppm	0.77 ppm	0.60 ppm	0.40 ppm	0.19 ppm	One-third the AEGL-3 Values
AEGL-3 (Lethality)	2.3 ppm	2.3 ppm	1.8 ppm	1.2 ppm	0.58 ppm	Threshold for lethality ($BMCL_{05}$) in female rats (Atochem, 1982)

ADMINISTRATIVE MATTERS

The next meeting of the NAC/AEGL will be held December 3-5, 2008, in SanDiego, CA.
The following meeting will be held March 3-5, 2009, in Alexandria, VA.

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 46 agenda
Attachment 2. Meeting 46 attendee list
Attachment 3. Phosgene new data presentation
Attachment 4. Ethyl benzene presentation
Attachment 5. n-Butyl isocyanate presentation
Attachment 6. Trimethylacetyl chloride presentation
Attachment 7. Germane Presentation
Attachment 8. Methyl parathion presentation
Attachment 9. Parathion presentation
Attachment 10. Phorate presentation
Attachment 11. tert-Octyl mercaptan presentation
Attachment 12. Meeting certification by Chair

LIST OF APPENDICES

Appendix A. Ballot for NAC-45 meeting summary
Appendix B. Final NAC-45 Meeting Highlights
Appendix C. Ballot for phosgene
Appendix D. Ballot for ethyl benzene
Appendix E. Ballot for n-butylisocyanate
Appendix F. Ballot for trimethylacetyl chloride
Appendix G. Ballot for germane
Appendix H. Ballot for methyl parathion
Appendix I. Ballot for parathion
Appendix J. Ballot for phorate
Appendix K. Ballot for tert-octyl mercaptan