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

December 3-5, 2008

Final Meeting-47 Highlights

Holiday Inn
1355 North Harbor Drive
San Diego, CA

INTRODUCTION

George Rusch opened the meeting which was followed by introductions of all participants.

The draft NAC/AEGL-46 meeting highlights were reviewed. A motion to accept the minutes as written was made by Dieter Heinz (second by Henry Anderson) and passed unanimously (Appendix A). The Final NAC/AEGL-46 meeting highlights are included as Appendix B.

Ernie Falke provided a status update on the National Academy of Science (NAS) publications. Volume 6 is published and additional volumes are under way. The Technical Support Document (TSD) and AEGL values for carbon monoxide can be finalized.

The highlights of the NAC/AEGL-47 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-47 Agenda.

STANDING OPERATING PROCEDURES (SOP) REVISIONS

Ernie Falke briefly described the status of the SOP addendum. The committee asked for a list of SOP issues at the next AEGL meeting. The Physiologically-Based Pharmacokinetic Modeling (PBPK) white paper will be posted on the AEGL website. In addition, TSD postings are under way. Only clean TSDs (not markup documents) will be posted on the AEGL website. The AEGL website is being revised and a new format will be posted in December. The committee requested to be informed when the new format is available. Therefore, an email will be sent to the committee members when the new website is available.

LOA DISCUSSION

The LOA paper is scheduled to be published as an RIVM publication in December and should be available on the website in 2009. Also, the paper will be sent to Don Gardner for publication in Inhalation Toxicology.

CHEMICAL LIST

There was considerable discussion regarding the source and criteria for chemicals to be considered for AEGL development. Possible criteria for adding a chemical to the priority list included sufficient vapor pressure, production and use data, and toxicity sufficient for concern. The NAC felt that it was important to know who was nominating chemicals for AEGL development and for what reasons. The committee also discussed putting together a guidance document listing chemical selection criteria and the possibility of publishing a list of tabled chemicals in an FR notice.

CHLOROSILANES GROUPING

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

Background information was provided by Cheryl Bast (Attachment 3). The NAC has developed AEGL values for 24 chlorosilanes. Twenty-one of these were developed at NAC-43 and NAC-44, are based on analogy to hydrogen chloride, and are presented in one TSD. The other three (dimethyldichloro-, trimethylchloro-, and methyltrichloro-silanes) were derived prior to NAC-43, are each presented in separate TSDs and values are based on chemical-specific data where available. The proposal is to incorporate all chlorosilanes into one TSD and use the HCl analogy approach for consistency. George Rusch recommended adding the derivation of the individual TSDs as an appendix in the new TSD. The revised TSD will contain all 24 chlorosilanes and derivation will be based on analogy to hydrogen chloride. The revised document should contain a discussion on the impact of bulky groups in the hydrolysis of the chlorosilane. Also, the revised document will include a table of the hydrolysis rates for the various chlorosilanes and will note those that do not have data. A motion (Marcel Van Raaij /John Hinz) was made to adopt the proposed AEGL values for the 3 chlorosilanes under consideration. The motion was approved unanimously (Appendix C: 22 yes; 0 no; 0 abstain).

Compound	Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
Trimethylchlorosilane	AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	Hydrogen chloride (HCl) AEGL-1 values adopted as AEGL-1 values (NRC, 2004)
	AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Hydrogen chloride (HCl) AEGL-2 values adopted as AEGL-2 values (NRC, 2004)
	AEGL-3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	Hydrogen chloride (HCl) AEGL-3 values adopted as AEGL-3 values (NRC, 2004)
Dimethyldichlorosilane	AEGL-1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	HCl AEGL-1 values divided by a molar adjustment factor of 2 adopted as AEGL-1 values (NRC, 2004)
	AEGL-2	50 ppm	22 ppm	11 ppm	5.5 pm	5.5 ppm	HCl AEGL-2 values divided by a molar adjustment factor of 2 adopted as AEGL-2 values (NRC, 2004)
	AEGL-3	310 ppm	110 ppm	50 ppm	13 ppm	13 ppm	HCl AEGL-3 values divided by a molar adjustment factor of 2 adopted as AEGL-3 values (NRC, 2004)
Methyltrichlorosilane	AEGL-1	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	0.60 ppm	HCl AEGL-1 values divided by a molar adjustment factor of 3 adopted as AEGL-1 values (NRC, 2004)
	AEGL-2	33 ppm	14 ppm	7.3 ppm	3.7 ppm	3.7 ppm	HCl AEGL-2 values divided by a molar adjustment factor of 3 adopted as AEGL-2 values (NRC, 2004)
	AEGL-3	210 ppm	70 ppm	33 ppm	8.7 ppm	8.7 ppm	HCl AEGL-3 values divided by a molar adjustment factor of 3 adopted as AEGL-3 values (NRC, 2004)

FEDERAL REGISTER 11- ACRYLONITRILE

Acrylonitrile (CAS No. 107-13-1) was the only chemical for which comments were received. Comments received from the AN Group on the FR submission for acrylonitrile were summarized by Robert Young (ORNL) (Attachment 4). The AN Group commended the NAC/AEGL for a thorough and thoughtful TSD. The AN Group suggested minor adjustment to uncertainty factor application resulting from PB-PK model results. Because the numerical adjustments were somewhat unorthodox relative to AEGL SOP guidelines and because the PB-PK model results were already incorporated into the development of the proposed AEGL values, it was decided unanimously to retain the original NAC/AEGL assessment. Additional reports regarding developmental/ reproductive studies on AN will be incorporated into the TSD as suggested by the AN Group. Consistent with AN suggestions, the cancer risk section will reflect current assessments of epidemiology reports and IARC decisions regarding no causal relationship for cancer risk from AN exposure. Bob Benson agreed to submit a write-up to this effect. George Woodall will offer the revision to the IRIS staff for comment.

ORGANOPHOSPHATE (OP) UNCERTAINTY FACTOR ISSUES

John Hinz and George Woodall led a discussion session on OP uncertainty issues in conjunction with a presentation (via teleconference) with Virginia Moser (U.S. EPA ORD) (Attachment 5). General information on the various targets of OPs and the metabolism of OPs were provided with respect to impact on interspecies and intraspecies uncertainty factors. Additionally, summary information for the specific OPs scheduled for discussion at the meeting were also provided. Although uncertainty factor selection and justification is always a chemical-specific issue, inhalation data on OPs are often very limited. Use of default uncertainty factors (currently 3 for interspecies and 10 for intraspecies) selection/justification will require careful consideration on a chemical-by-chemical basis.

CHEMICAL REVISITS/STATUS UPDATES

No Data Chemicals

Cheryl Bast (ORNL) provided a status update for aluminum chloride, antimony pentafluoride, phosphorus pentafluoride, and phosphorus pentasulfide. These chemicals have no data and will be placed in holding status.

The committee commented on the 12 chemicals that did not have AEGL values (as described in the NAC-46 highlights). The following recommendations were made:

a. Identify criteria for chemical selection and publish it in the addendum of the SOP. This suggestion was made by Calvin Willhite.
b. Publication of tabled chemicals in a FR notice requesting additional data for AEGL development.
c. Refer chemicals to groups that have a structure-activity background.

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

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

A status update was provided by Sylvia Talmage. Industry is still working on the PBPK modeling results for methyl iodide.

Allyl Alcohol (CAS No. 107-18-6)

Staff Scientist: Claudia Troxel, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Bob Benson, the chemical manger, made brief introductory remarks on this chemical. The chemical has been considered by the NAC and reviewed by the COT multiple times. At the December, 2006, NAC meeting, Dr. Marcy Banton, a representative of Lyondell, the sole US manufacturer of allyl alcohol, offered to ask her company to sponsor an additional study to help resolve the issues that led to the lack of agreement by the COT of the AEGL values derived by the NAC. Dr. Banton was successful in her effort. The new study was completed earlier this year. Dr. Jeff Fowles, the present representative of Lyondell Basell, presented a brief summary of the results of this new study (Attachment 6). Claudia Troxel then began a discussion of the data available on the chemical and the reasons for the previous lack of agreement between the NAC and COT on the AEGL values (Attachment 7). New AEGL-3 values were derived based on the LC_{01} from all the rat studies showing lethality using the ten Berge regression program with n = 0.95 and a total uncertainty factor of 10 (3 each for interspecies and intraspecies extrapolation). The values are 260 ppm, 82 ppm, 40 ppm, 9.3 ppm, and 4.5 ppm for 10 minutes to 8 hours, respectively. AEGL-2 values were calculated by deriving the AEGL-3 values by 3 because the NOEL for severe, irreversible nasal lesions was virtually identical to the exposure-

response relationship for lethality. The AEGL-2 values are 87 ppm, 27 ppm, 13 ppm, 3.1 ppm, and 1.5 ppm for 10 minutes to 8 hours, respectively. John Hinz moved that the AEGL-3 and AEGL-2 values be accepted. Mark Baril seconded the motion. The motion passed (Appendix D: 19 yes; 0 no; 1 abstain). Possibilities for AEGL-1 values included the human data for eye irritation from a 5 minute exposure with values of 2.1 for 10, 30, and 60 minutes, and Not Recommend for longer durations; the new laboratory animal study in rats showing nasal inflammation 14 days after exposure (9.3 ppm, 6.4 ppm, 5.1 ppm, 2.2 ppm, and 1.0 ppm for 10 minutes to 8 hours, respectively); the new laboratory animal study in rats showing nasal degeneration 14 days after exposure (21 ppm, 21 ppm, 6.8 ppm, 0.68 ppm, and 0.21 ppm for 10 minutes to 8 hours, respectively); and the new laboratory animal study in rats showing a lessening of the startle response during exposure (14 ppm, 5.3 ppm, 3.2 ppm, 0.9 ppm, and 0.5 ppm for 10 minutes to 8 hours, respectively. Bob Benson made the motion to accept the values based on nasal inflammation. George Woodall seconded the motion. The motion passed (Appendix D: 20 yes; 0 no; 0 abstain).

These discussions identified an SOP issue regarding analysis of data using the ten Berge program and whether to report only the 1% response or lower limit of the 5% response.

Summary of AEGL Values for Allyl Alcohol						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL−1 (Nondisabling)	9.3 ppm	6.4 ppm	5.1 ppm	2.2 ppm	1.0 ppm	Nasal inflammation in rats (Kirkpatrick, 2008)
AEGL−2 (Disabling)	87 ppm	27 ppm	13 ppm	3.1 ppm	1.5 ppm	Severe, irreversible lesions in rats (Kirkpatrick, 2008)
AEGL−3 (Lethal)	260 ppm	82 ppm	40 ppm	9.3 ppm	4.5 ppm	LC_{01} (Combined rat data)

REVIEW of PRIORITY CHEMICALS

Tear Gas (CAS No. 2698-41-1)

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

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for tear gas (Attachment 8). Proposed AEGL-1 values were based on human exposure to 1.5 mg/m^3 for 90 minutes (Punte et al., 1963), an exposure tolerated by all 4 subjects but resulting in ocular and nasal irritation and headache. One subject developed nasal irritation within 2 minutes, three subjects developed headache (at 45, 50, and 83 minutes), and all four experienced ocular irritation (at 20, 24, 70, and 75 minutes). The intraspecies uncertainty factor was limited to 3 because contact irritation is a portal-of-entry effect and is not expected to vary widely among individuals and was supported by the fact that responses of volunteers with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed to a highly irritating concentration of CS for short durations (Punte et al., 1963; Gutentag et al., 1960). The interspecies uncertainty factor was 1 was due to the use human data. A modifying factor of 10 was applied to reduce the point-of-departure from

a LOEL to a NOAEL for effects defined by AEGL-1. Time scaling was not applied in the development of the AEGL-1 values, because the critical effect (irritation) is a function of direct contact with the tear gas and is not likely to increase with duration of exposure at this level of severity (NRC, 2001). The AEGL-2 values were based on the same point-of departure as the AEGL-1 values. Uncertainty factor application was the same as for the AEGL-1 derivation described above. However, no modifying factor was applied in the derivation of AEGL-2 values, because the observed effects meet the definition of AEGL-2. The AEGL-2 values were held constant across time. The AEGL-3 values were based on the threshold for lethality at each AEGL-3 exposure duration calculated using the probit-analysis based dose-response program of ten Berge (2006). The assessment used rat lethality data (McNamara et al., 1969; Ballantyne and Calloway, 1972; Ballantyne and Swantson, 1978) and the LC_{01} as the benchmark. The analysis showed a time-scaling value of 0.704 ($C^{0.704} \times t = k$). The 4-hour AEGL-3 value was adopted as the 8-hour AEGL-3 value because time scaling yielded an 8-hour value inconsistent with the AEGL-2 values that were derived from a rather robust human data set. Inter- and intraspecies uncertainty factors of 3 each were applied (total 10) and were considered sufficient because clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals. The interspecies UF of 3 is supported by calculated LCt_{50} values of 88,480 mg min/m^3 for rats; 67,200 mg min/m^3 for guinea pigs; 54,090 mg min/m^3 for rabbits; and 50,010 mg min/m^3 for mice (Ballantyne and Swantson, 1978), values all well within a factor of two. The intraspecies UF of 3 is supported by the fact that responses of volunteers with jaundice, hepatitis, or peptic ulcer or those that were 50-60 years old were similar to those of "normal" volunteers when exposed to highly irritating concentration of CS for short durations (Punte et al., 1963; Gutentag et al., 1960).

A motion by John Hinz (Dieter Heinz second) to accept the values as proposed including AEGL-1 values of 0.05 mg/m^3 for all durations passed unanimously (Appendix E: 21 yes; 0 no; 0 abstain). The AEGL-2 motion also passed (Appendix E: 21 yes; 0 no; 0 abstain), as did the AEGL-3 (Appendix E: 19 yes; 1 no; 1 abstain).

Summary of AEGL Values for Tear Gas

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.050 mg/m^3	0.050 mg/m^3	0.050 mg/m^3	0.050 mg/m^3	0.050 mg/m^3	Ocular/nasal irritation and headache in humans (Punte et al., 1963)
AEGL–2 (Disabling)	0.50 mg/m^3	0.50 mg/m^3	0.50 mg/m^3	0.50 mg/m^3	0.50 mg/m^3	Ocular/nasal irritation and headache in humans (Punte et al., 1963)
AEGL–3 (Lethal)	140 mg/m^3	29 mg/m^3	11 mg/m^3	1.5 mg/m^3	1.5 mg/m^3	Threshold for lethality (LC_{01}) in rats [McNamara et al.(1969); Ballantyne and Calloway (1972); and Ballantyne and Swantson (1978)]

Ricin (CAS No. 9009-86-3)

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

Robert Young summarized the data for ricin noting that inhalation data are especially limited and that there are critical issues regarding variable potency of such a toxin (Attachment 9). Data are unavailable with which to derive AEGL-1 values and, therefore, they are not recommended (motion by john Hinz, second by Jim Holler; Appendix F: 22 yes, 0 no, 0 abstain). AEGL-2 values were initially derived based upon data in rats showing changes in pulmonary function following a single acute exposure but it was noted that this approach was tenuous. Specifically, rats exposed to a Ct of 16.7 mg•min/m^3 (≈LC_{25}; considered sublethal by the investigators) showed a mild inflammatory response of insufficient severity to cause fluid accumulation in the lung or to seriously compromise the gas exchange process. The assessment was conducted at 30 hours post exposure which the investigators considered an estimated time for peak injury. Although the investigators reported no serious compromise in the gas exchange process in the lungs of the exposed rats, the arterial oxygen saturation appeared to be somewhat lower than that of unexposed controls (85% vs 90%; not statistically significant) and the exposure was noted as an LC_{25}. It was the consensus of the NAC-AEGL that this was a tenuous approach and that no AEGL-2 values be derived (motion by John Hinz, second by Jim Holler; Appendix F: 22 yes, 0 no, 0 abstain). The AEGL-3 values were based upon rat lethality data reported by Griffiths et al. (1995a). Analysis of these data using the U.S. EPA Benchmark Dose software (U.S. EPA, 2008) was limited or not possible due to varying exposure durations. Software of ten Berge (2006) was provided point estimates (LC_{01}) of 0.88, 0.28, 0.13, 0.031, and 0.0015 mg/m^3, respectively, for the 10-minute, 30-minute, 1-hour, 4-hour, and 8-hour AEGL time frames based upon an exposure duration-exposure concentration relationship (ln concentration vs. ln minutes) of 0.95. These values were decreased 2.7-fold due to known variability in the potency of the ricin preparations tested. Uncertainty application used interspecies and intraspecies factors of 3 each for a total of 10. Experimental exposure durations in all of the animal studies were very short (minutes). The exposure durations used to generate the data for AEGL-3 analysis ranged from 6 to 12 minutes. Due to uncertainties in extrapolating from these very short exposure durations, 4-hour and 8-hour AEGL-3 values were not recommended. Following discussions focusing on the limited data and variable potency, the AEGL-3 values of 0.033, 0.010, and 0.0048 mg/m^3 for the 10-min, 30-min. and 1-hr, respectively were adopted (Appendix F: 15 yes; 3 no; 1 abstain) following a motion by John Hinz and seconded by Jim Holler. Concern was expressed regarding the validity of 1-hour values based upon data limited to exposure duration of only several minutes.

AEGL Values for ricin (mg/m^3)						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-3 (Lethality)	0.033	0.010	0.0048	NR	NR	estimated lethality threshold (LC_{01}) in rats (Griffiths et al., 1995a); values incorporate a 2.7-fold reduction for potency variability; UF=10 (3x3); n=0.95

Dichlorvos (CAS No. 62-73-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: John Hinz, AFIOH/RSRE

Jennifer Rayner provided a review of the available data and draft AEGL values (Attachment 10). The draft AEGL-1 values were based on clinical exposure data showing that humans exposed for 2-7 hours to ~0.11 ppm (1 mg/m^3) dichlorvos experienced only inhibition of plasma cholinesterase activity (Hunter 1970a). The POD was 0.11 ppm (1 mg/m^3) and supported by an occupational exposure data where workers exposed to an average concentration of 0.078 ppm (0.7 mg/m^3) dichlorvos for 8 months experienced inhibition of plasma and erythrocyte cholinesterase activity but experienced no adverse health effects during or 4 months following exposure (Menz et al., 1974). The interspecies uncertainty factor for AEGL-1 was 1 because human data were used, and the intraspecies uncertainty factor was 1 based on oral and inhalation human data showing no sex-, age-, compromised health status-related differences in response to dichlorvos exposure. Following discussions, the data from Hunter (1970a) was selected as the AEGL-1 values for all durations (motioned by Bob Benson; seconded by Dieter Heinz; vote 18 yes, 3 abstain, 0 no). The AEGL-2 values were based on a POD of 0.56 ppm (5 mg/m^3) for rats exposed for 45 min (Atis et al. 2002). At 1.1 and 1.7 ppm (10 and 15 mg/m^3), the rats experienced dyspnea, increased salivation, excessive urination and defecation, and alveolar degeneration but at 0.56 ppm there were no clinical signs of toxicity. This exposure, however, did cause a shortening of epithelial cells in the trachea, loss of cilia from the ciliated cells of the trachea as well as alveolar interstitial thickening, capillary congestion, and extravasated erythrocytes. The POD was the highest experimental value without an AEGL-2 effect. This POD was also based on a 2-yr study in rats (Blair et al. 1976). The rats were exposed to dichlorvos 23 hr/d and exhibited no signs of organophosphate toxicity at 0.56 ppm (5 mg dichlorvos (vapor)/m^3) but male rats did have decreased body weight, consistently 20% or more of control male rats from the 10th week of treatment until termination. The AEGL-2 values were kept constant across all time points because the 2-yr study showed that prolonged exposure would not result in an enhanced effect. The interspecies uncertainty factor for AEGL-1 was 1 because experimental data showed that humans are no more sensitive and possibly less sensitive than laboratory animals to dichlorvos, and the intraspecies uncertainty factor was 1 based on oral and inhalation human data showing no sex-, age-, compromised health status-related differences in response to dichlorvos exposure. Additionally, as AEGL values are set for vapor concentrations, the Blair et al. (1976) vapor study shows that the POD is protective of the population. The AEGL-2 values of 0.56 ppm (5 mg/m^3) for all time points was unanimously approved (motion by Bob Benson, second by Calvin Willhite, vote: 19 yes; 0 no; 2 abstain). AEGL-3 values were not initially derived but, following committee deliberation, were based upon the highest nonlethal exposure of (8 ppm [72 mg/m^3] for 16 hrs) in a study by Dean and Thorpe (1972a). The interspecies uncertainty factor for AEGL-1 was 1 because experimental data showed that humans are no more sensitive and possibly less sensitive than laboratory animals to dichlorvos, and the intraspecies uncertainty factor was 1 based on oral and inhalation human data showing no sex-, age-, compromised health status-related differences in response to dichlorvos exposure. The AEGL-3 values of 8.0 ppm (72 mg/m^3) for all time points was approved motion by Bob Benson, second by John Hinz, Appendix G: 15 yes; 0 no; 6 abstain)

AEGL Values for dichlorvos (ppm)						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.11	0.11	0.11	0.11	0.11	No effects in human volunteers exposed for 2-7 hours to 0.11 ppm (1 mg/m^3) (Hunter 1970a)
AEGL-2 (Disabling)	0.56	0.56	0.56	0.56	0.56	Highest experimental exposure without an AEGL-2 effect (0.56 ppm, 5 mg/m^3) (Atis et al. 2002)
AEGL-3 (Lethality)	8.0	8.0	8.0	8.0	8.0	Highest experimental exposure without a lethal effect (8.0 ppm, 72 mg/m^3) (Dean and Thorpe 1972a)

Dicrotophos (CAS No. 141-66-2)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Robert Young provided an overview of the inhalation data for this chemical (no human data and only two studies in rats) with an emphasis on the marginal nature thereof (Attachment 11). Data were not available for derivation of AEGL-1 values and AEGl-2 values. Data from one study suggested a steep exposure-response relationship which was used to justify draft AEGL-2 values as a 3-fold reduction of the AEGL-3 values. AEGL-3 values were initially based upon 1–hour and 4-hour LC_{50} value both of which were 90 mg/m^3. After a brief discussion of the data and their limitations, it was moved by Bob Benson to defer further discussion of this chemical to the next meeting and reconsider dicrotophos in conjunction with monocrotophos. A motion to this effect was made by Bob Benson, second by Calvin Willhite, and passed unanimously by a show of hands.

Fenamiphos (CAS No. 22224-92-6)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: George Woodall, U.S. EPA

Jennifer Rayner provided a brief overview the limited data for this chemical (Attachment 12). An attempt will be made to obtain a non-sanitized copy of a Bayer Corp. study (Thyssen, 1979) on the 4-hr exposure of rats which may of use in developing AEGL values. If obtained, these data may be used for 4-hr BMC analysis and ten Berge calculations. Further deliberations on this chemical were tabled (unanimous vote by show of hands).

Malathion (CAS No. 121-75-5)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: John Hinz, AFIOH/RSRE

Carol Wood presented an overview of the draft TSD for malathion (Attachment 13). AEGL-1 and AEGL-2 were based upon data from a subchronic inhalation study in Sprague-Dawley rats (US EPA 2000) exposed to malathion (96.4% a.i.) aerosols (in air) at concentrations of 0, 100, 450 or 2010 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. The 6-hour exposure to 450 mg/m^3 was chosen as the POD for derivation of AEGL-1 values. Because clinical signs at the point of departure were sporadic and cholinesterase activity inhibition was not biologically significant after the 13-week exposure, time scaling was not performed. The total uncertainty factor of 30 includes 10 for intraspecies extrapolation to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases and 3 for interspecies extrapolation to account for the differences in serum carboxylesterase levels between humans and rata. The 2010 mg/m^3 exposure for 6 hours was the POD for AEGL-2 values. Critical effects after 13-week exposure included microscopic lesions and significant inhibition of brain cholinesterase activity. A total uncertainty factor of 30 was applied as for AEGL-2 with time scaling using default values of n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point (30-minute value was adopted as the 10-minute AEGL-2 value as per AEGL SOP). A motion to accept the AEGL-1 and AEGL-2 values as presented was made by Bob Benson and second by Jim Holler. The motion passed (Appendix H: 21 yes, 0 no, 0 abstain). AEGL-3 values for malathion were not recommended in the draft TSD. Following discussion, the NAC/AEGL decided to base AEGL-3 values on a POD of 6900 mg/m^3 (5-hr exposure) which represented the highest exposure for any species. The uncertainty factor application (total of 30) and time scaling (default) were as for AEGL-1 and AEGL-2. AEGL-3 values (expressed as mg/m^3) of 500, 500, 390, 250, and 140 for 10-min, 30-min, 1-hr- 4-hrs, and 8-hrs, respectively were adopted (motion by Bob Benson, second by Jim Holler; Appendix H: 16 yes; 2 no; 3 abstain). It was decided to include a footnote for the AEGL-3 values noting that lethal air concentrations are unavailable for humans and animals and that lethal air concentrations may not be attainable.

AEGL Values for Malathion

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	Sporadic clinical signs in rats (US EPA 2000)
AEGL–2 (Disabling)	150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3	Clinical signs in rats (US EPA 2000)
AEGL–3* (Lethal)	500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3	6900 mg/m^3 (5-hr exposure); highest available exposure for any species

* Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malathion may not be possible.

Mevinphos (CAS No. 7786-34-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Daniel Sudakin, Oregon St. Univ.

Jennifer Rayner reviewed the extremely limited information on this chemical (Attachment 14). The low vapor pressure of mevinphos likely precludes significant inhalation exposure and route-

to-route extrapolation may be considered. The possibility of a position paper on route-to-route extrapolation was discussed. The SOP addressed this issue but does not provide specific guidance on procedures/methods. Paul Tobin will work with OPP to come up with a scientific approach for the pesticides of AEGL concern. Gail Chapman also mentioned the availability of cholinesterase inhibition data in one of the mevinphos papers and queried how these data might be used in the mevinphos assessment. Deliberation on mevinphos was deferred until "credible" route-to-route extrapolation procedures are investigated.

Bromoacetone (CAS No. 598-31-2)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Roberta Grant, TX Commission Environ. Quality

Cheryl Bast presented an overview of the data and draft AEGL values (Attachment 15). Proposed AEGL-1 values were based on a concentration causing ocular irritation in 2/6 humans (0.1 ppm) (Dow Chemical, 1968). 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 irritation) is a function of direct contact with the bromoacetone vapor and not likely to increase with duration of exposure (NRC, 2001). However, because of the lack of human data beyond a few seconds, a modifying factor of 3 was applied. Although the concentration-response relationship for bromoacetone is not particularly steep, the AEGL-3 values were divided by 3 to derive proposed AEGL-2 values for bromoacetone. This approach was utilized because use of the rat irritation data as a point-of-departure yields AEGL-2 values essentially identical to AEGL-3 values calculated from lethality data.

Proposed AEGL-3 values were based on rat lethality data of varying exposure concentrations and durations (Dow Chemical, 1968). Experimental concentrations ranged from 1 to 131 ppm and durations ranged from 6 to 120 minutes. The threshold for lethality at each AEGL-3 exposure duration was calculated 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 1.256 ($C^{1.256} \times t = k$). These calculated values were used as the basis for the AEGL-3 values. Inter- and intraspecies uncertainty factors of 3 each were applied (total 10) and are considered sufficient because bromoacetone is an irritant (lacrimation, nasal discharge, gasping, wheezing, and labored breathing in rats and ocular irritation in humans; Dow Chemical, 1968) and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Calvin Willhite suggested mentioning chloroacetone in the structure-activity section of the TSD. A motion was made by Calvin Willhite (second by Gail Chapman) to adopt the AEGL values as presented. The motion passed (Appendix I: 19 yes; 0 no; 0 abstain).

AEGL Values for Bromoacetone (ppm)						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm	0.011 ppm	Ocular irritation in humans (Dow Chemical, 1968)
AEGL–2 (Disabling)	1.4 ppm	0.57 ppm	0.33 ppm	0.11 ppm	0.063 ppm	One-third the AEGL-3 Values
AEGL–3 (Lethal)	4.1 ppm	1.7 ppm	0.98 ppm	0.32 ppm	0.19 ppm	Threshold for lethality (LC_{01}) in rats (Dow Chemical, 1968)

Phosphorus Pentachloride (CAS No. 10026-13-8)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: Bob Benson, U.S. EPA

Bob Benson, chemical manager, made brief introductory remarks. Carol Wood, author of the TSD, then presented a discussion of the inhalation data available for the chemical (Attachment 16). The human data consisted of a case report of an industrial accident, a laboratory animal study available only in a secondary report, and another laboratory animal study with only limited experimental details presented (Molodkina, 1973). After a brief discussion of the feasibility of using data on PCl_3 or $POCl_3$ to derive values for PCl_5, Bob Benson moved that the chemical be place in holding status and request that ORNL try to obtain additional information from the producer of the chemical. Dieter Heinz seconded the motion. The motion was approved unanimously by non-ballot vote (Appendix J).

Nitrogen Trifluoride (CAS No. 7783-54-2)

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

Bob Benson, chemical manager, made brief introductory remarks. Sylvia Talmage, author of the TSD, then presented a discussion of the inhalation data available for the chemical (Attachment 17). There are no human data available. However, there is a fairly robust data set in laboratory animals with lethality studies in four species with less than a two-fold difference in response. There are also repeat-exposure and subchronic studies in rats, developmental/reproductive studies in rats, and genotoxicity studies. For AEGL derivation the primary effect is the formation of methemoglobin. Data from the dog, the most appropriate species, was used to derive all AEGL values. For all values an interspecies UF of 1 and an intraspecies UF of 10 were used. Time scaling was done with the experimentally derived n = 1 from the lethality studies using the ten Berge (2006) regression analysis program. Draft AEGL-1 values for the formation of 15% methemoglobin were 1200 ppm, 400 ppm, 200 ppm, 50 ppm, and 25 ppm for 10 minutes to 8 hours, respectively. Draft AEGL-3 values for the formation of 70% methemoglobin were 5000 ppm, 1700 ppm, 860 ppm, 220 ppm, and 110 ppm for 10 minutes to 8 hours, respectively. Draft AEGL-2 values were derived by averaging AEGL-1 and AEGL-3

values and correspond to the formation of 42% methemoglobin with values of 3100 ppm, 1100 ppm, 530 ppm, 140 ppm, and 68 ppm for 10 minutes to 8 hours, respectively. Aniline methemoglobin information was used as a reference for nitrogen trifluoride. Bob Benson moved that these values be accepted. Mark Baril seconded the motion. The motion passed (Appendix K: 19 yes; 0 no; 1 abstain).

AEGL Values for Nitrogen Trifluoride (ppm)						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL−1 (Nondisabling)	1200 ppm	400 ppm	200 ppm	50 ppm	25 ppm	≤15% methemoglobin formation in monkeys and dogs following 60-minute exposure to 2000 ppm (Vernot et al. 1973)
AEGL−2 (Disabling)	3100 ppm	1100 ppm	530 ppm	140 ppm	68* ppm	Estimated 43% methemoglobin in dogs: midpoint of AEGL-1 and AEGL-3 (Vernot et al. 1973)
AEGL−3 (Lethal)	5000 ppm	1700 ppm	860 ppm	220 ppm	110 ppm	Regression analysis of dog lethality data of Vernot et al. (1973) calculated with the ten Berge (2006) program

*Due to a typographical error in presentation material, the balloted value was 55 ppm.

ADMINISTRATIVE MATTERS

Future Meetings:
April 14-16, 2009 in Alexandria, VA.
September 9-11, 2009 (Paris, Montreal or Denver)
December 2-4, 2009 (perhaps Orlando, Florida)

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, and Bob Benson and Iris Camacho, U.S. EPA.

LIST OF ATTACHMENTS

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

Attachment 1. Meeting 47 agenda
Attachment 2. Meeting 47 attendee list
Attachment 3. Chlorosilanes presentation
Attachment 4. Acrylonitrile response to FR comments presentation
Attachment 5. OP issues-Virginia Moser presentation
Attachment 6. Allyl alcohol- LyondelleBasell/Fowles
Attachment 7. Allyl alcohol presentation- Troxel/Benson
Attachment 8. Tear gas presentation
Attachment 9. Ricin presentation
Attachment 10. Dichlorvos presentation
Attachment 11. Dicrotophos presentation
Attachment 12. Fenamiphos presentation
Attachment 13. Malathion presentation
Attachment 14. Mevinphos presentation
Attachment 15. Bromoacetone presentation
Attachment 16. Phosphorus pentachloride presentation
Attachment 17. Nitrogen trifluoride presentation
Attachment 18. NAC- 47 meeting certification

LIST OF APPENDICES

Appendix A. Ballot for approval of NAC-46 meeting highlights
Appendix B. Final NAC-46 Meeting Highlights
Appendix C. Ballot for chlorosilanes
Appendix D. Ballot for allyl alcohol
Appendix E. Ballot for tear gas
Appendix F. Ballot for ricin
Appendix G. Ballot for dichlorvos
Appendix H. Ballot for malathion
Appendix I. Ballot for bromoacetone
Appendix J. Ballot for phosphorus pentachloride
Appendix K. Ballot for nitrogen trifluoride