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

April 12-14, 2005

Final Meeting-36 Highlights

U.S. EPA, Office of Research and Development
Building C, Auditorium
109 T.W. Alexander Drive
Research Triangle Park, NC 27709

INTRODUCTION

Chairman George Rusch welcomed the committee and thanked George Woodall for the meeting arrangements. Dr. Tim Oppelt, Acting Director of the U.S. EPA Office of Research and development, welcomed the group to Research Triangle Park

George Rusch informed the committee that Dr. Doan Hansen, former Department of Energy representative to the NAC/AEGL, had died from a heart attack on March 12, 2005.

The draft NAC/AEGL-35 meeting highlights were reviewed. John Morawetz provided several comments, especially with regard to human data descriptions and including more detail documenting the history of AEGL definition issues. Marc Ruijten suggested editorial corrections These suggestions were incorporated into the highlights. A motion was made by Marc Ruijten and seconded by Richard Thomas to accept the meeting highlights as presented with the aforementioned revisions. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-35 meeting highlights is attached (Appendix B).

The highlights of the NAC/AEGL-36 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-36 Agenda.

REVIEW OF NAS/COT-15 (February, 2005) MEETING

Ernest Falke and George Rusch reviewed process/procedure issues discussed at NAS/COT-15; resolution of these issues is designed to improve productivity (rate of publication). Currently, the NAS/COT subcommittee has published 24 "final" AEGL TSDs. The NAC has completed 139 chemicals. Dr. Don Gardner, the new NAS/ COT subcommittee chair, has a goal of finalizing 20 chemicals each year. In order to accomplish this goal, the following items were suggested (1)

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limit all chemicals to three COT reviewers; (2) limit each TSD to two visits to COT; (3) improve dialog/come to closure at the meeting (reviewers can't push open-ended issues); (4) resolve conflicting reviewer comments prior to publication of the interim report; (5) shorten the TSD length (delete non-essential references/study descriptions); and (6) clarify the application of uncertainty factors (UFs) and modifying factors (MFs) (see below).

Iris Camacho then discussed issues relating to the NAC/AEGL Standing Operating Procedures (SOPs) (Attachment 3). Among the SOP issues discussed at NAS/COT-15 were rounding of the time scaling exponent 'n' and use of UFs and MFs.

The NAS/COT agreed that, where data allow, round empirically-derived values of the exponent 'n' to two significant figures. After a short discussion, a motion was made by John Hinz and seconded by George Woodall to adopt this suggested approach for derivation of the time scaling exponent. The motion passed unanimously by a show of hands (Appendix C).

The NAS/COT subcommittee expressed concerns on the current approach used to justify/adjust UFs downward from the default value of 10, because often it is not possible to assign the adjustment between inter- and intraspecies variability. The NAS/COT suggested applying the default UFs unless there are data showing that interspecies or intraspecies differences merit a reduction (adhere strictly to SOP in these cases). Then, if the overall data base suggests that values are too low, apply an alternate factor (e.g. MF) for adjusting the AEGL values to be consistent with the human and/or animal supporting data. Another approach recommended to the NAC/AEGL by Iris Camacho was to create the weight-of-evidence factor (WOEF). This approach would not change the AEGL values, but the derivation would be more transparent and consistent. The magnitude of the weight-of-evidence factor would be >0. Values less than 1 should be expressed as a fraction such as 1/3 or 1/10, to be consistent with the UF progression of 1, 3, and 10, and to avoid a repeating decimal. The rationale for the weight-of-evidence factor should include citations and explanations of the supporting human and/or animal data; and justification for the selected factor, including discussion of why the initially-derived AEGL values conflict with published data.

Thorough discussion centered around an acceptable name for the alternate factor, modifying the definition of UFs and modifying the definition of MFs. Ursula Gundert-Remy agreed with the proposal for the WOEF, but recommended being cautious about using the expression "data-derived UF". In addition, she asked how this new factor would consider kinetic/dynamic differences. Bob Benson also agreed with using a WOEF, because it is makes the derivations more transparent. Tom Hornshaw asked whether there was a precedence within EPA for use of a WOEF. Bob Benson indicated that the EPA's IRIS program has a provision to allow a modifying factor < 1. Jonathan Borak found the term WOEF confusing and felt it would conflict with the cancer terminology; he supported the concept of an adjustment factor. Kowetha Davidson mentioned that there are provisions in EPA's RfD guidelines to allow MF <1. Marc Ruijten suggested revisiting the UF definitions in the SOP so UFs<1 are allowed. Richard Thomas favored revising the MF definition to allow a MF<1; he did not like the term WOEF. Marc Ruijten said that the WOEF would confirm the reasonableness of the values; he supports the

WOEF if restricted to such purpose. Ursula Gundery-Remy recommended separating the MF from WOEF.

George Rusch then suggested analyzing UF rationales of final and interim TSDs where UFs<10 were utilized in order to be consistent with supporting data. He favored a data-adjustment factor applied to the total UF value because it would allow more flexibility to use an UF of 3 or 1. Analysis of UF rationales of final and interim documents will show where the NAC has deviated from the SOP thus far, and may provide information helpful in revising/expanding the UF definitions/applications in the SOP. The chemical managers were tasked to evaluate the UF justifications in their chemicals and to provide this information to Iris Camacho or Ernest Falke before the June, 2005, meeting. The UF application sections of the SOP could then be revised where appropriate, and this approach will be presented to the NAS/COT subcommittee. Marc Ruijten supported George Rusch's suggestion because SOP definitions are too restricted. In addition, he suggested eliminating the two SOP sections that deal with adjusting the inter- and the intraspecies UF in order to be consistent with the empirical data, redefining the inter- and intraspecies UFs. George Woodall stated that EPA has an uncertainty factor data base in preparation; he will provide Iris Camacho with appropriate information from this data base.

The key points of this discussion are as follows: (1) do not expand the MF definition;
(2) analyze UF usage and then revise the SOP; (3) create a 4th factor that takes into consideration professional judgement/weight-of-evidence. (All NAC members raised their hands when asked if they favored the creation of such a factor).

SOP PBPK White Paper

Jim Dennison presented information concerning the use of PBPK modeling in AEGL value development ("The White Paper") (Attachment 4). After approval by the NAC and COT AEGL subcommittee, this guidance may become part of the revised SOP. Major discussion points included application of the UF before or after the dose metric and choice of workload parameters. The following guests from EPA, RTP were present for the discussion: Marina Evans, Will Boyes, Paul Schlosser, Jane-Ellen Simmons, and Vernon Benignus. Will Boyes advocated applying the UF at the end of the PBPK analysis, and suggested that chemical assessment should be separated from policy. Vernon Benignus stated that if a PK model was validated in both humans and an animal species, the UF would equal 1, and that applying a dose adjustment factor at step 4 in the model creates a policy decision. Paul Schlosser stated that if it is assumed that humans and animals respond at the same target concentration, then the interspecies UF should be applied at the end of the PBPK analysis. Jane Ellen Simmons suggested looking at blood concentrations in multiple species where data are available. Ursula Gundery-Remy said that more discussion on the dynamic component in the white paper is needed to avoid the idea that the kinetic information is predicting the dynamic component. Ursula stated that the ACUTEX program does not consider sensitive populations in the analysis. George Rusch asked the committee whether they favored applying the UF at an intermediate step or at the end of the calculations. There was more general support for UF application in the middle of the assessment. Marc Ruijten suggested including the

workload information in an appendix (as is done for carcinogenicity) and not to consider workload for derivations.

Time will be set aside at the June meeting to compare examples of AEGL values derived by PBPK modeling and the traditional approach utilizing a key study and endpoint and time scaling. These examples will include examples with and without workload.

CHEMICAL PRIORITY LIST

Marquea King discussed the revised AEGL chemical priority list (Attachment 5). Current sources and strategies for identifying priority AEGL chemicals were reviewed. Also discussed was the fact that the SOP contains provisions for modifying the chemical priority list. NAC members suggested the following additional sources for identifying potential priority chemicals: FBI, NOA-CAMEO, and HPV/OECD. George Rusch suggested that the DOE TEELs be provided, rather than IDLH values, on the chemical list. After this discussion, Marquea King requested that NAC members provide her with any additional feedback on the chemical priority list within one month.

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

Comments from the *Federal Register Notice* of September 7, 2004, on the proposed AEGL values for epichlorohydrin and acetone were reviewed and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

Epichlorohydrin (CAS No. 106-89-8)

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

Comments from the *Federal Register Notice* on the proposed AEGL values for epichlorohydrin were reviewed and discussed by Kowetha Davidson (Attachment 6). Comments were received from Ernest Falke who commented that the odor threshold should not be used as support for AEGL-1 and that secondary sources should not be used for derivation of AEGL values. Two options were presented. Proposal No. 1 was to use the UCC (1983) report showing pharyngeal irritation in one of four subjects exposed to 68 ppm epichlorohydrin for 2 minutes. Exposure to 136 ppm resulted in ocular and pharyngeal irritation in two of the four subjects. Application of an intraspecies UF of 3 to the POD of 68 ppm and time scaling using n= 0.87, would result in a 10-min AEGL-1 value of 3.6 ppm. This value would be adopted for all time points (mild irritation). Proposal No. 2 was to not recommend AEGL-1 values. After discussion, a motion was made by Marc Ruijten and seconded by George Woodall to base AEGL-1 values on a NOEL for irritation in humans exposed to 17 ppm epichlorohydrin for 2 minutes (UCC, 1983). An uncertainty factor

of 3 was applied, and the resulting value of 5.7 ppm would be adopted at all time points (mild irritation). The motion carried (YES:16; NO: 0; ABSTAIN: 0) (Appendix D). John Morawetz and Kowetha Davidson will work together to revise descriptions of human studies.

Summary of Interim AEGL-1 Values for Epichlorohydrin					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	5.7 ppm	5.7 ppm	5.7 ppm	5.7 ppm	5.7 ppm	NOAEL for irritation in humans (UCC, 1983)

Acetone (CAS No. 67-64-2)

Staff Scientist: Jens-Uwe Voss
Chemical Manager: Nancy Kim, State of New York

Comments from the *Federal Register Notice* on the proposed AEGL values for acetone were reviewed and discussed by Ursula Gundert-Remy (Attachment 7). Comments were received from the Global Acetate Manufacturers Association (GAMA) and John Morawetz (ICUWC). Gama commented on all three AEGL tiers. Comments on AEGL-2 and AEGL-3 values suggested using human case report data and PBPK modeling rather than using animal data. AEGL-1 comments from GAMA included the selection of an "outdated" key study, non-conformance with the SOP regarding sensory irritation (acetone is a mild sensory irritant and proposed AEGL-1 values are too low), and the AEGL-1 values and LOA very close to one another. Mr. Morawetz was concerned with the POD selected for AEGL-1; he felt that the POD was a threshold, not a NOAEL for irritation, and thus an additional modifying factor may be appropriate. Also, of the 4 studies used for AEGL-1, Mr. Morawetz felt that the Nelson (1943) study was not appropriate because of only nominal exposure/methodology issues. Also, this study was not considered appropriate for derivation of AEGL values for acetylaldehyde. After much discussion, a motion was made by Bob Benson and seconded by George Rodgers to raise the proposed AEGL values for acetone to interim status. The motion carried (YES: 15; NO: 0; ABSTAIN: 0) (Appendix E). The Nelson study will be removed as support for AEGL-1.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS ON THE INTERIM AEGL VALUES

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

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

Claudia Troxel discussed the data set and COT/AEGL's comments (Attachment 8). The COT/AEGL had two main areas of concern: (1) selection of an interspecies UF of 1 in the derivation of AEGL-3 values; and (2) rounding of the experimentally-derived value of n = 0.8 to n = 1 is not consistent with the SOP. Susan Ripple informed the committee that Dow Chemical has unpublished data that may impact the derivation of AEGL values for allyl alcohol. Thus, this chemical was deferred to a future NAC meting so that the Dow data may be evaluated and included in the TSD if appropriate.

Iron Pentacarbonyl (CAS No. 13463-40-6)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Ernest Falke, U.S. EPA

Bob Young discussed the data set and COT/AEGL's comments (Attachment 9). The COT/AEGL had one main area of concern: the derived value of n = 1 for time scaling AEGL-3 values. This value of n = 1 was developed based upon the similarity of Ct products using one 30-minute rat LC_{50} value and one 4-hour rat LC_{50} value. Due to a paucity of data, the COT suggested using the default time scaling values of n = 1 or n = 3. Using this approach, proposed AEGL-3 values were 0.33 ppm, 0.23 ppm, 0.18 ppm, 0.11 ppm, and 0.075 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. These revised values are more protective than the originally proposed values but are justified by the SOP. The AEGL-2 values (1/3 of AEGL-3 values) are also adjusted accordingly. After discussion, a motion was made by Richard Thomas and seconded by Ernest Falke to adopt AEGL-3 values as proposed, except that the 30-minute value should be adopted as the 10-minute value because the POD was 4-hours. The motion carried (YES: 16; NO: 1; ABSTAIN: 1) (APPENDIX F).

Summary of AEGL Values for Iron Pentacarbonyl						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Not Recommended
AEGL–2	0.077 ppm	0.077 ppm	0.060 ppm	0.037 ppm	0.025 ppm	1/3 the AEGL-3 values
AEGL–3	0.23 ppm	0.23 ppm	0.18 ppm	0.11 ppm	0.075 ppm	$BMCL_{05}$ for death in rats (BASF, 1995)

Ammonia (CAS No. 7664-41-7)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Kowetha Davidson discussed the data set and COT/AEGL's comments (Attachment 10). Mr. William Herz, Director of Scientific Programs, The Fertilizer Institute was present for the

discussion. The COT/AEGL had five main areas of concern: (1) selection of intraspecies UFs for AEGL-1, AEGL-2, and AEGL-3; (2) Interspecies UF for AEGL-3; (3) derivation of 5-minute AEGL values; (4) revision of the summary of the Verberk (1977) study; and (5) Selection of the POD for AEGL-2.   After discussion, the NAC decided to retain current uncertainty factors but to strengthen/clarify the justifications. NAC members should send any suggestions for strengthening these justifications to Dr. Davidson for inclusion in the TSD, and she will send the response to George Rusch, Ernest Falke, and Susan Ripple for review. The NAC also decided not to include 5-minute AEGL values and to revise the description of the Verberk study by expanding the experiment table in the TSD. After more discussion regarding derivation of AEGL-2 values, a motion was made by Steve Barbee and seconded by Richard Thomas to adopt AEGL-2 values of 220 ppm, 220 ppm, 160 ppm, 110 ppm, and 110 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. These values are based on irritation in humans exposed to 110 ppm for 2 hours (Verberk, 1977).   An intraspecies UF of 1 was applied because unbearable irritation was not observed in this study until the concentration reached 140 ppm. Time scaling was accomplished utilizing $n = 2$ derived from mouse and rat lethality data. The 4-hour value was adopted as the 8-hour value because the maximum severity rating for irritation (Verberk, 1977) changed very little between 1 and 2 hours and thus is not expected to change from 4- to 8-hours. The 30-min value was also adopted as the 10-min AEGL-2 value because time scaling would yield a 10-min value (380 ppm) that might impair escape. Values are supported by data of Cole et al. (1977) and Silverman et al. (1949) showing no serious irreversible effects at 336 ppm or 500 ppm, respectively. The motion carried (YES: 10; NO: 4; ABSTAIN: 3) (APPENDIX G).

Summary of AEGL-2 Values for Ammonia						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–2	220 ppm	220 ppm	160 ppm	110 ppm	110 ppm	NOAEL for irritation in humans (Verberk, 1977)

Acrylic Acid (CAS No. 79-10-7)

Staff Scientist: Peter Griem, FOBIG
Chemical Manager: Ernest Falke, U.S. EPA

Ursula Gundert-Remy discussed the data set and COT/AEGL's comments (Attachment 11). The COT/AEGL had three main areas of concern: (1) suitability of the Renshaw data for basis of AEGL-1; (2) time scaling exponent, n, was derived from lethality data from an aerosol exposure (AEGL-2 values); and (3) AEGL-3 values should be based on vapor, not aerosol, data. After discussion, the NAC decided to resubmit the Renshaw data to the COT and support the AEGL-1 POD with the Lomax et al. (1994) study showing that 5 ppm, 6 hours/day for 2 weeks was a NOEL for histopathology in mice. AEGL-3 values will remain based on the aerosol data, but the

BASF (1980) vapor data will be used as support (show of hands). A motion was then made by Marc Ruijten and seconded by Ernest Falke to retain and again present the current AEGL-2 values (68 ppm, 68 ppm, 46 ppm, 21 ppm, and 14 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) to the COT and to give the staff scientist the authority to provide AEGL-2 values utilizing the default exponent of $n = 1$ or $n = 3$ (66 ppm, 45 ppm, 36 ppm, 19 ppm, and 9.4 ppm) for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively as an acceptable set of alternate AEGL-2 values if the COT continues to reject the originally-derived values. The two sets of values are similar to one another. The motion carried (YES: 16; NO: 0; ABSTAIN: 0) (APPENDIX H).

REVIEW of PRIORITY CHEMICALS

Methyl t-butyl Ether (CAS No. 1634-04-4)

Staff Scientist: Dana Glass, ORNL
Chemical Manager: Steve Barbee, Arch Chemical

Dana Glass reviewed the available data for methyl t-butyl ether (MTBE) (Attachment12). Proposed AEGL-1 values (50 ppm at all time points) were based on the highest NOEL reported in humans (50 ppm for 2 hours; Nihlen et al., 1998). No UF was applied because the POD was a NOEL in humans. Values were held constant across all time periods. Proposed AEGL-2 values (1400 ppm, 1400 ppm, 980 ppm, 400 ppm, and 400 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on transient central nervous system effects in rats exposed to 4000 ppm for 6 hours (Daughtrey et al., 1997). An interspecies UF of 3 was proposed because PBPK modeling data suggest that humans have a 1.5 to 2.5-fold increase of MTBE concentration in blood compared to rats. An intraspecies UF of 3 was also proposed because variability of CNS depression is no greater than 3-fold in the human population. Time scaling was accomplished using an exponent of $n = 2$, based on rat and mouse lethality data. The 4-hour value was proposed as the 8-hour value because steady state is achieved by 2 hours in the rat and 4 hours in humans. The 30-min value was proposed as the 10-min value because the POD was >4 hours. Proposed AEGL-3 values (7500 ppm, 7500 ppm, 5300 ppm, 2700 ppm, and 1900 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a 4-hour rat $BMCL_{05}$ (ARCO, 1978). Inter- and intraspecies UFs of 3 each were applied as for AEGL-2. Time scaling was accomplished with $n = 2$, as for proposed AEGL-2 values. It was noted that PBPK data were not sufficient for derivation of AEGL values, but blood partition data could be used to justify UFs. After discussion, a motion was made by Richard Niemier and seconded by Marc Ruijten to adopt AEGL-1 values as proposed and to support the intraspecies UF of 1 with rat data showing no effects at 400 ppm and only minor effects at 4000 ppm for 6 hours. The motion carried (YES: 17; NO: 0; ABSTAIN: 0) (APPENDIX I).

A motion was then made by Richard Niemier and seconded by John Hinz to adopt AEGL-2 values of 1400 ppm, 800 ppm, 570 ppm, 400 ppm, and 400 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on a POD of 4000 ppm for 2 hours. This POD is derived from the transient central nervous system effects in rats exposed to 4000 ppm for 6 hours (Daughtrey et al., 1997). However, because data show that steady state is achieved in 2 hours in the rat, the

two hour time point was assumed valid for the point of departure. Time scaling was achieved using n = 2 for the 10-min, 30-min, 1- hr and 4-hr time points. The 4-hour value was adopted as the 8-hour value because steady-state is achieved in the human within 4 hours. The motion carried (YES: 15; NO: 1; ABSTAIN: 1) (APPENDIX I).

Marc Ruijten then contacted Dr. ten Berge and obtained the raw rat and mouse lethality data used to derive the n = 2 value. These data supported the ARCO (1978) data proposed as the basis of AEGL-3 values and also support the interspecies UF of 3 because the rat and mouse data are similar. A motion was then made by Marc Ruijten and seconded by George Rodgers to accept the AEGL-3 values as proposed except that the 10-minute AEGL-3 value will be time scaled because the n value was derived from data ranging from 3 minutes to 4 hours. This 10-min AEGL-3 value (13,000 ppm will be listed as a footnote because it is $10% of the LEL. The motion carried (YES: 14; NO: 0; ABSTAIN: 0) (APPENDIX I).

Summary of AEGL Values for Methyl t-Butyl Ether						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	50 ppm	50 ppm	50 ppm	50 ppm	50 ppm	NOEL in humans (Nihlen et al., 1998)
AEGL–2	1400 ppm	800 ppm	570 ppm	400 ppm	400 ppm	Transient CNS effects in rats (Daughtrey et al., 1997)
AEGL–3	¶13,000 ppm	7500 ppm	5300 ppm	2700 ppm	1900 ppm	$BMCL_{05}$ for death in rats (ARCO, 1978)

¶The value is higher than 10% of the lower explosive limit of MTBE in air . Therefore, safety considerations against the hazard of explosion must be taken into account.

Hexafluoroacetone (CAS No. 684-16-2)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Bob Young reviewed the available data for hexafluoroacetone (HFA) (Attachment13). AEGL-1 values were not recommended because of insufficient data. Proposed AEGL-2 values (0.076 ppm, 0.076 ppm, 0.061 ppm, 0.038 ppm, and 0.025 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a NOAEL of 1.0 ppm (6 hrs/day on gestation days 7-16) for developmental toxicity in rats (du Pont, 1989). The higher tested dose (6.9 ppm) resulted in a significantly increased incidence of malformations, an increase in total resorptions/litter, a decrease in the number of liver fetuses/litter, and decreased fetal weight. It was assumed that the effects could be induced by a single 6-hr exposure. An interspecies UF of 10 was proposed because there were data from only one animal species. An intraspecies UF of 3 was proposed because HFA does not appear to undergo significant metabolism and because the fetus is

considered a uniquely sensitive target. Time scaling was accomplished using the default values of n =1 or n =3. The 30-min value was proposed as the 10-min value because the POD was 6-hours. Proposed AEGL-3 values (19 ppm, 13 ppm, 11 ppm, 6.7 ppm, and 3.3 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively) were based on a NOAEL for lethality in rats (200 ppm for 4 hours) (duPont, 1962). An interspecies UF of 10 was proposed because there were data from only one animal species. An intraspecies UF of 3 was proposed because HFA does not appear to undergo significant metabolism and because further downward reduction would result in AEGL-3 values below proposed AEGL-2 values and below non nonlethal concentrations in multiple-exposure studies in rats and dogs. Time scaling was accomplished using the default values of n =1 or n =3. During deliberations, a suggestion was made to calculate a $BMDL_{05}$ for the developmental effects proposed as the basis of AEGL-2. However, the raw data needed for this calculation were unavailable. After more discussion, a motion was made by George Rodgers and seconded by Susan Ripple to not recommend AEGL-1 values for HFA due to insufficient data. The motion carried (YES: 14; NO: 0; ABSTAIN: 0) (APPENDIX J). A motion was then made by Tom Hornshaw and seconded by Bob Benson to accept AEGL-3 values of 160 ppm, 160 ppm, 80 ppm, 20 ppm, and 10 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on the proposed POD of 200 ppm for 4 hours (NOEL for death in rats). Uncertainty factors of 3 each (total = 10) will be applied for inter- and intraspecies extrapolation. The justification for the intraspecies UF is as proposed above, and reducing the proposed interspecies UF from 10 to 3 is supported by multiple exposure studies in rats and dogs and the fact that HFA is not metabolized (is direct acting). Time scaling will be accomplished using n = 1, calculated by Marc Ruijten using the ten Berge program. The 30-min AEGL-3 value will be adopted as the 10-min value because the POD is $4 hours. The motion carried (YES: 15; NO: 1; ABSTAIN: 0) (APPENDIX J). A motion was then made by Bob Benson and seconded by John Hinz to adopt AEGL-2 values of 0.4 ppm, 0.4 ppm, 0.2 ppm, 0.05 ppm, and 0.025 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively, based on the proposed POD of 1.0 ppm for 6 hours (developmental effects in rats). Uncertainty factor application and time scaling are the same as utilized for AEGL-3 derivation. An attempt will be made to obtain the raw data from the duPont study and calculate a $BMCL_{05}$ for the developmental toxicity data. Bob Young will report on this at a later meeting, and AEGL-2 values may be adjusted, if necessary. The motion carried (YES: 13; NO: 1; ABSTAIN: 3) (APPENDIX J).

Summary of AEGL Values for Hexafluoroacetone						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Appropriate data not available
AEGL–2	0.40 ppm	0.40 ppm	0.20ppm	0.05 ppm	0.025 ppm	NOEL for developmental effects in rats (duPont, 1989)
AEGL–3	160 ppm	160 ppm	80 ppm	20 ppm	10 ppm	NOEL for death in rats (duPont, 1962)

NR: Not Recommended because of insufficient data.

Aluminum Phosphide (CAS No. 20859-73-8)

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

Cheryl Bast reviewed the available data for aluminum phosphide, a solid (Attachment14). One mole of aluminum phosphide reacts rapidly with water or moisture in air to produce one mole of phosphine gas, and it is the phosphine gas that is responsible for acute toxicity. Appropriate chemical-specific data are not available for derivation of AEGL values for aluminum phosphide. In the absence of appropriate chemical-specific data for aluminum phosphide, the AEGL-2 and AEGL-3 values for phosphine were proposed as surrogates to obtain AEGL-2 and AEGL-3 values for aluminum phosphide, respectively. The use of phosphine as a surrogate for aluminum phosphide was deemed appropriate because qualitative (clinical signs) and quantitative (phosphine blood level) data suggest that the phosphine hydrolysis product is responsible for acute toxicity from aluminum phosphide. It was proposed that the phosphine AEGL-2 values be adopted as AEGL-2 values for aluminum phosphide and the phosphine AEGL-3 values be adopted as AEGL-3 values for aluminum phosphide. Values will be expressed as ppm or mg/m^3 phosphine. AEGL-1 values are not recommended for aluminum phosphide because data were insufficient for derivation of AEGL-1 values for phosphine. After discussion, a motion was made by Bob Benson and seconded by John Hinz to adopt AEGL values as proposed. The motion passed (YES: 16; NO: 1; ABSTAIN: 1) (Appendix K).

It was then pointed out that seven additional metal phosphides are on the AEGL chemical priority list. A TSD for "Selected Metal Phosphides" will be prepared and presented at a future meeting. The aluminum phosphide values and analysis will be included in this TSD, and may be published in the same COT volume with the phosphine TSD.

Summary of AEGL Values for Aluminum Phosphide (EXPRESSED AS PPM OR MG/M³ PHOSPHINE)*						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Appropriate data not available
AEGL-2	4.0 ppm (5.6 mg/m^3)	4.0 ppm (5.6 mg/m^3)	2.0 ppm (2.8 mg/m^3)	0.50 ppm (0.71 mg/m^3)	0.25 ppm (0.35 mg/m^3)	Phosphine AEGL-2 values adopted as aluminum phosphide AEGL-2 values (NAC/AEGL, 2004).
AEGL-3	7.2 ppm (10 mg/m^3)	7.2 ppm (10 mg/m^3)	3.6 ppm (5.1 mg/m^3)	0.90 ppm (1.3 mg/m^3)	0.45 ppm (0.63 mg/m^3)	Phosphine AEGL-3 values adopted as aluminum phosphide AEGL-3 values (NAC/AEGL, 2004).

NR: Not Recommended

Nitrogen Mustards
HN-1 (CAS No. 538-07-8)
HN-2 (CAS No. 5107502)
HN-3 (CAS No. 555-77-1)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Richard Thomas, INTERCET

Bob Young reviewed the available data for the nitrogen mustards (Attachment 15). No AEGL-1 values were proposed because of insufficient data and the absence of detection at exposures capable of causing toxic responses. Proposed AEGL-2 values for HN1, HN2, and HN3 were based upon the upper range of eye injury thresholds from studies with human volunteer subjects; 90, 55, and 42 mg-min/m^3, respectively, for HN1, HN2, and HN3. Proposed AEGL-2 values were: HN1: 0.90 ppm, 0.30 ppm, 0.15 ppm, 0.038 ppm, and 0.019 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN2: 0.55 ppm, 0.18 ppm, 0.092 ppm, 0.023 ppm, and 0.011 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN3: 0.42 ppm, 0.14 ppm, 0.070 ppm, 0.018 ppm, and 0.0088 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. The ocular response is likely independent of dosimetric processes that would be relevant to systemically-mediated toxicity. Therefore, the proposed uncertainty factor for individual variability was limited to 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects; therefore, modifying factor of 3 was applied to account for possible effects on the respiratory tract. Where AEGL-2 time points coincided with the exposure duration range used to establish the threshold Ct, time-specific exposure concentrations for proposed AEGLs were calculated from the Ct value. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 or 3 was used in the equation, $C^n \times t = k$, for extrapolating to AEGL time periods not within the range of experimental exposure duration.

Lethality thresholds (LCt$_{50}$) for rats were used as the basis for proposed AEGL-3 values; 860, 2000, and 670 mg-min/m^3 for HN1, HN2, and HN3, respectively. Proposed AEGL-3 values were: HN1: 2.9 ppm, 0.96 ppm, 0.48 ppm, 0.12 ppm, and 0.060 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN2: 6.7 ppm, 2.2 ppm, 1.1 ppm, 0.28 ppm, and 0.14 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr; HN3: 2.2 ppm, 0.74 ppm, 0.37 ppm, 0.093 ppm, and 0.047 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively). These specific LCt$_{50}$ values were based upon experimental exposure durations ranging from 20-100 minutes (HN1), 120-360 minutes (HN2), and 10-100 minutes (HN3) and, therefore considered suitable for AEGL development. Consistent with AEGL methodology (NRC, 2001), a three-fold reduction of these lethality values was used as an estimate of the lethality threshold and the point-of-departure for AEGL-3 development. A total uncertainty factor of 10 was applied. Adjustment for interspecies variability was limited to 3 because LCt$_{50}$ values among multiple species (including nonhuman primates) did not appear to vary by more than three-fold for each agent, and the rat was somewhat more sensitive. Adjustment for individual variability was limited to 3 because the action of nitrogen mustards on cellular components would not be expected to greatly differ, and because additional downward adjustment would result in proposed AEGL-3 values inconsistent

with proposed AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard). An experimentally-derived n of 1 was used in the equation, C^n x t = k, for extrapolating to AEGL time periods.

Marc Ruijten expressed concern with deriving AEGL values for these compounds because of the poor data base. He felt that this approach will set a precedence and will remove incentive for conducting new experiments and providing new data.

After discussion, a motion was made by Bob Benson and seconded by John Hinz to not recommend AEGL-1 values for HN1, HN2, and HN3. The motion passed unanimously by a show of hands. A motion was then made by George Rodgers and seconded by George Woodall to adopt AEGL-2 values for HN1 using the lower level of the range (37 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN1 of 0.37 ppm, 0.12 ppm, 0.062 ppm, 0.015 ppm, and 0.0077 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed.   A motion was then made by George Woodall and seconded by George Rodgers to adopt AEGL-2 values for HN2 using the lower level of the range (40 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN2 of 0.13 ppm, 0.044 ppm, 0.012 ppm, 0.0056 ppm, and 0.0028 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed. A motion was then made by George Rodgers and seconded by Nancy Kim to adopt AEGL-2 values for HN3 using the lower level of the range (20 mg-min/m^3) for ocular effects in humans as the point-of-departure. Uncertainty factor application and time scaling remained as proposed. This approach yielded AEGL-2 values for HN3 of 0.20 ppm, 0.067 ppm, 0.033 ppm, 0.0083 ppm, and 0.0042 ppm for 10-min, 30-min, 1-hr, 4-hr and 8-hr, respectively. This motion passed. A motion was then made by Richard Thomas and seconded by Richard Niemier to adopt the most conservative set of AEGL-2 values (HN2 AEGL-2 values) as AEGL-2 values for all of the nitrogen mustards. All individually-derived chemical-specific values are to presented in an appendix to the TSD. The motion passed (YES: 12; NO: 1; ABSTAIN: 3) (Appendix L).

A motion was made by Richard Thomas and seconded by Richard Niemier to adopt AEGL-3 values for HN1 as proposed. The motion passed. A motion was then made by Richard Niemier and seconded by John Hinz to adopt the AEGL-3 values for HN2 and HN3 as proposed. The motion passed. Finally, a motion was made by Tom Hornshaw and seconded by Richard Niemier to adopt the most conservative set of AEGL-3 values (HN3 AEGL-3 values) as AEGL-3 values for all of the nitrogen mustards. All individually-derived chemical-specific values are to presented in an appendix to the TSD. The motion passed (YES: 10; NO: 1; ABSTAIN: 5) (Appendix L).

Summary of AEGL Values for Nitrogen Mustards						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not Recommended
AEGL–2	0.13 ppm	0.044 ppm	0.022 ppm	0.0056 ppm	0.0028 ppm	Lower limit of range for ocular irritation in humans sufficient to compromise operational effectiveness (Porton Report 1942a, 1943d; U.S. Army Med. Div. 1945c, d.)
AEGL–3	2.2 ppm	0.74 ppm	0.37 ppm	0.093 ppm	0.047 ppm	Lethality threshold in rats estimated as 3-fold reduction of LCt_{50} values (Porton Report. 1943b,c; U.S. Army Med. Div., 1945a)

Methylchlorosilane (CAS No. 993-00-0)

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

Cheryl Bast discussed the available data (Attachment 16). Methylchlorosilane reacts rapidly with water or moisture and decomposes to form hydrogen chloride gas. Complete hydrolysis of one mole of methylchlorosilane would yield a maximum of one mole of hydrogen chloride. No human or animal data on methylchlorosilane are available. Although chemical-specific data are not available for methylchlorosilane, data from structurally-similar alkyl-substituted silicon tetrahydrides [dimethyldichlorosilane (Dow Corning, 1997a), methyltrichlorosilane (Dow Corning,1997b) , trimethylchlorosilane (Dow Corning, 1999a), and methyldichlorosilane (Dow Corning, 2001)] suggest that the acute toxicity of chlorosilanes is due to the hydrogen chloride hydrolysis product. These data suggest that the effects of hydrogen chloride and chlorosilanes are both quantitatively (based on molar equivalents of hydrogen chloride) and qualitatively (based on clinical signs) similar. Therefore, proposed AEGL-1, AEGL-2 and AEGL-3 values for methylchlorosilane were set equivalent to the hydrogen chloride AEGL-1, AEGL-2, and AEGL-3 values (NRC, 2004), respectively. This approach was considered valid because one mole of hydrogen chloride is produced for every mole of methylchlorosilane hydrolyzed. A motion was then made by Richard Thomas and seconded by Steve Barbee to adopt AEGL-1, AEGL-2 and AEGL-3 values as proposed, The motion passed (YES: 16; NO: 0; ABSTAIN: 0) (Appendix M).

Summary of AEGL Values for Methyl chlorosilane						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	Hydrogen Chloride AEGL-1 values adopted as methylchlorosilane AEGL-1 values (NRC, 2004)
AEGL–2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm	Hydrogen Chloride AEGL-2 values adopted as methylchlorosilane AEGL-2 values (NRC, 2004)
AEGL–3	620 ppm	210 ppm	100 ppm	26 ppm	26 ppm	Hydrogen Chloride AEGL-3 values adopted as methylchlorosilane AEGL-3 values (NRC, 2004)

Methyldichlorosilane (CAS No. 75-54-7)

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

Cheryl Bast discussed the available human and animal data (Attachment 17). Methyldichlorosilane reacts vigorously and rapidly with water and decomposes to form hydrogen chloride; complete hydrolysis of one mole of methyldichlorosilane would yield a maximum of two moles of hydrogen chloride. In the absence of appropriate chemical-specific data for derivation of AEGL-1 and AEGL-2 values for methyldichlorosilane, a modification of the AEGL-1 and AEGL-2 values, respectively, for hydrogen chloride was proposed to derive AEGL-1 and AEGL-2 values for methyldichlorosilane. The use of hydrogen chloride as a surrogate for methyldichlorosilane was deemed appropriate because the hydrolysis product, HCl, is responsible for the acute toxicity. Since two moles of hydrogen chloride are produced for every mole of methyldichlorosilane hydrolyzed, a molar adjustment factor of 2 was applied to the hydrogen chloride AEGL-1 and AEGL-2 values to approximate proposed AEGL-1 and AEGL-2 values for methyldichlorosilane. Proposed AEGL-3 values were based on a calculated LC_{01} of 1400 ppm in rats exposed to methyldichlorosilane for 1 hour (Dow Corning, 2001). An uncertainty factor of 10 was proposed to account for interspecies variability since data for methyldichlorosilane were available for only one species and an uncertainty factor of 3 was proposed to account for sensitive human subpopulations. Time scaling was accomplished using $n = 1$ (experimentally-derived value for HCl) for periods up to 4-hr. The 4-hour AEGL-3 value was adopted as the 8-hour value because time scaling would yield an 8-hour AEGL-3 value inconsistent with the total data set. After discussion, a motion to accept the AEGL values as

proposed was made by Richard Niemier and seconded by John Hinz. The motion carried (YES: 12; NO: 2; ABSTAIN: 0) (Appendix N).

Summary of AEGL Values for Methyldichlorosilane						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	0.90 ppm	Modification of Hydrogen Chloride AEGL-1 values (NRC, 2004)
AEGL–2	50 (235)	22 (103)	11(52)	5.5 (26)	5.5 (26)	Modification of Hydrogen Chloride AEGL-2 values (NRC, 2004)
AEGL–3	280 (1316)	93 (437)	47 (220)	12 (56)	12 (56)	1 hour LC_{01} in rats (Dow Corning, 2001)

Diketene (CAS No. 674-82-8)

Staff Scientist: Kowetha Davidson, ORNL
Chemical Manager: Warren Jederburg, U.S. Navy

Kowetha Davidson discussed the available data (Attachment 18). After some discussion, a motion was made by George Rodgers and seconded by George Woodall to Table this chemical until the September, 2005, NAC meeting when the structurally-similar chemical, ketene, is scheduled for presentation. Also, the BMC concentrations for diketene will be recalculated using the analytical, not nominal concentrations. The motion carried (YES: 15; NO: 0; ABSTAIN: 0) (Appendix O).

ADMINISTRATIVE MATTERS

 The site and time of future meetings is as follows:

NAC/AEGL-37: June 13-15, 2005, Washington DC
NAC/AEGL-38: September 28-30, 2005, Washington DC

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

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-36 Meeting Agenda
Attachment 2. NAC/AEGL-36 Attendee List
Attachment 3. SOP Issues
Attachment 4. PBPK White Paper
Attachment 5. Revised Chemical Priority List
Attachment 6. Response to Federal Register comments for epichlorohydrin
Attachment 7. Response to Federal Register comments for acetone
Attachment 8. Response to COT comments for allyl alcohol
Attachment 9. Response to COT comments for iron pentacarbonyl
Attachment 10. Response to COT comments for ammonia
Attachment 11. Response to COT comments for acrylic acid
Attachment 12. Data analysis for methyl t-butyl ether
Attachment 13. Data analysis for hexafluoroacetone
Attachment 14. Data analysis for aluminum phosphide
Attachment 15. Data analysis for nitrogen mustards
Attachment 16. Data analysis for methylchlorosilane
Attachment 17. Data analysis for methyldichlorosilane
Attachment 18. Data analysis for diketene

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Appendix P. AEGL Committee Chairman Certification of Minutes