

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

December 12-14, 2006

Meeting-41 Highlights

**Hilton-Old Town/Alexandria
1767 King Street
Alexandria, VA 22314**

INTRODUCTION

Chairman George Rusch welcomed the committee, and thanked Drs. Marc Ruijten and Wil ten Berge for conducting a workshop on the DoseResp software. The workshop was held prior to the NAC meeting (December 11, 2006) and was well attended by both NAC members and ORNL staff. The increased familiarity with the software and methods should help with future AEGL value development. George Rusch informed the committee that Dr. Elaine Krueger, NAC member representing the Massachusetts Department of Health, died as a result of cancer. Paul Tobin then read a summary of Dr. Krueger's professional background, and a moment of silence followed. Martha Steele will be the Massachusetts Department of Health representative on the NAC starting in June, 2006.

The draft NAC/AEGL-40 meeting highlights were reviewed. A motion was made by Henry Anderson and seconded by Dieter Heinz to accept the minutes as written. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-40 meeting highlights is attached (Appendix B).

The highlights of the NAC/AEGL-41 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-41 Agenda.

REVIEW of FEDERAL REGISTER-09 COMMENTS

Forty seven chemicals were included in the FR09 publication. Those not receiving comments are elevated to interim status. Chemicals elevated to interim status include:

Acetaldehyde (75-07-0), Benzonitrile (100-47-0), Bromine pentafluoride (7789-30-2), Bromine trifluoride (7787-71-5), Butadiene (106-99-0), Butane (106-97-8), Chlorine pentafluoride (13637-63-3), Chloroacetaldehyde (107-20-0), Chloroacetone (78-95-5), Chloroacetyl chloride (79-04-9), Cumene (98-82-8), Dichloroacetyl chloride (79-36-7), Dimethyl sulfate (77-78-1), Disulfur dichloride (10025-67-9), Ethyl mercaptan (75-08-1), Hexane (110-54-3), Hydrogen bromide (10035-10-6), Hydrogen iodide (10034-85-2), Hydrogen selenide (7783-07-5), Lewisite L-1 (541-25-3), Lewisite L-2 (40334-69-8), Lewisite L-3 (40334-70-1), Methacrylonitrile (126-98-7), Methyl bromide (74-83-9), Methyl chloride (74-87-3), Methylene chloride (75-09-2), Oleum (8014-95-7), Piperidine (110-89-4), Propane (74-98-6), Propionaldehyde (123-38-6), Sulfur trioxide (7446-11-9), Sulfuric acid (7664-93-9), and Vinyl chloride (75-01-4).

Comments received will be discussed at the current meeting with the exception of five aliphatic nitriles which will be discussed at NAC-42 (March, 2007). Ernie Falke announced that there are a total of 285 priority chemicals. There are approximately 100 chemicals that still need to be addressed by the NAC. Several of these chemicals will be addressed by chemical class, and production/use information will be obtained to determine if it is prudent to address all remaining chemicals.

Ethyl Acrylate (CAS No. 140-88-5)

Butyl Acrylate (CAS No. 141-32-2)

Staff Scientist: Carol Wood, ORNL

Chemical Manager: George Woodall, U.S. EPA/ Ursula Gundert-Remy, Germany

Comments were received from the Basic Acrylic Monomers Manufacturers, Inc. (BAMM). Comments stated that the proposed AEGL values are scientifically appropriate and fully protective of human health. A motion was made by Richard Thomas and seconded by George Rodgers to elevate ethyl acrylate (Appendix C) and butyl acrylate (Appendix D) to interim status. The motion passed unanimously by a show of hands.

Formaldehyde (CAS No. 50-00-0)

Staff Scientist: Sylvia Talmage, ORNL

Chemical Manager: George Rodgers

Comments received from the Formaldehyde Council were reviewed by Sylvia Talmage (Attachment 3). The comments stated that the AEGL values represent the lower end of reasonable values. Discussion focused on AEGL-1 (value of 0.9 ppm at all time points implies a level of precision not supported by the data) and AEGL-3 values (possibility of revising time scaling). After a thorough discussion, a motion was made by Marc Ruijten and seconded by Richard Niemeier to elevate the formaldehyde AEGL values to interim. The motion carried unanimously (YES: 21; NO: 0; ABSTAIN: 0) (APPENDIX E).

AEGL-41

Titanium Tetrachloride (CAS No. 7550-88-3)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: Jim Holler, ATSDR

Claudia Troxel reviewed Comments from Lyondell Chemical Company (Attachment 4). Comments suggested having NR for AEGL-1 values because the proposed AEGL-2 values should be adequately protective for the AEGL-1 endpoint. Proposed AEGL-1 values were based on a no-effect-level in a 4-week repeated-exposure rat study. Discussion focused on the possibility of deriving AEGL-1 values by molar equivalence analogy to hydrogen chloride (i.e. one mole of titanium tetrachloride will yield 4 moles of HCl upon complete hydrolysis). However, this approach was not adopted because titanium tetrachloride may be more than 4-fold as toxic as hydrogen chloride. A motion was made by George Woodall and seconded by Ernest Falke to adopt NR for AEGL-1 values due to insufficient data. The motion passed by a show of hands (YES: 20; NO: 0; ABSTAIN: 1) (APPENDIX F). A motion was then made by John Hinz and seconded by Jim Holler to elevate proposed AEGL-2 and AEGL-3 values and NR for AEGL-1 to interim status. The motion passed by a show of hands (YES: 20; NO: 0; ABSTAIN: 1) (APPENDIX F).

Benzene (CAS No. 71-43-2)

Staff Scientist: Marcel vanRaaij, RIVM
Chemical Manager: Robert Snyder, Rutgers Univ.

Marc Ruijten reviewed the benzene comments on behalf of Marcel vanRaaij (Attachment 5). Comments were received from John Morawetz. Several editorial comments will be incorporated into the document. Technical comments focused on occupational studies used in a weight-of-evidence approach for AEGL-3 derivation; Mr. Morawetz had made similar comments at the June, 2003, NAC meeting, and these issues were discussed at that time. A motion was made by Ernest Falke and seconded by Bob Benson to elevate the proposed benzene AEGL values to interim status. The motion passed (YES: 19; NO: 0; ABSTAIN: 1) (APPENDIX G).

Methacrylic Acid (CAS No. 79-41-4)

Staff Scientist: Fritz Kalberlah, FOBIG
Chemical Manager: Robert Benson, U.S. EPA

Chemical manager Bob Benson presented comments on methacrylic acid from the Methacrylate Producers Association (MPA) (Attachment 6). MPA was in general agreement with the proposed AEGL values. A motion was made by George Rodgers and seconded by Richard Niemeier to elevate the proposed AEGL values for methacrylic acid to interim status. The motion passed unanimously by a show of hands (APPENDIX H).

AEGL-41

Methyl Methacrylate (CAS No. 80-62-6)

Staff Scientist: Fritz Kalberlah, FOBIG

Chemical Manager: Robert Benson, U.S. EPA

Chemical manager Bob Benson presented comments on methyl methacrylate from the Methacrylate Producers Association (MPA) (Attachment 6). The MPA was in general agreement with the proposed AEGL-1 values. A motion was made by George Rodgers and seconded by Richard Niemeier to elevate the AEGL-1 values from proposed to interim status. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). MPA commented that the AEGL-2 was too low because there were no serious effects noted in humans at concentrations above 300 ppm; MPA suggested deriving AEGL-2 values by dividing the AEGL-3 values by 3. After discussion, the NAC found no valid reason to reject high quality animal studies and adopt a default procedure. A motion was made by Richard Thomas and seconded by John Hinz to elevate the proposed AEGL-2 values to interim status. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). MPA commented that the proposed AEGL-3 values were too low as a result of the BMD from the Tansy study (POD for proposed AEGL-3) being too low compared to other animal data. The MPA suggested reducing the uncertainty factor. After extensive discussion and consideration of six options/approaches (Attachment 6), a motion was made by Dieter Heinz and seconded by Bob Benson to adopt AEGL-3 values of 720 ppm for 10- and 30-minutes, 570 ppm for 1 hour, 360 ppm for 4-hours, and 180 ppm for 8-hours based on a BMCL05 of 3613 ppm for a single 6-hr rat exposure from the combined data of Tansy et al., (1980) and NTP (1986). The total uncertainty factor is 10, and time scaling used the default n values of 1 or 3. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix H).

| Summary of AEGL-3 Values for Methyl Methacrylate | | | | | | |
|--|-----------|-----------|---------|---------|---------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-2 | 720 ppm | 720 ppm | 570 ppm | 360 ppm | 180 ppm | 4-hr BMCL05 in rats (Tansy et al., 1980; NTP, 1986) |

Styrene (CAS No. 80-62-6)

Staff Scientist: Jens-Uwe Voss, Chemrisk, Germany

Chemical Manager: Lynn Beasley, U.S. EPA

Ernest Falke presented comments on styrene from the Styrene Information and Research Center (SIRC) (Attachment 7). None of the comments will affect the AEGL values; however,

AEGL-41

incorporation of the comments will provide a more complete TSD. A motion was made by George Woodall and seconded by John Hinz to elevate the proposed AEGL values for styrene to interim status. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix J). George Woodall is the IRIS chemical manager for styrene, and will help with the TSD revision.

REVIEW of COT COMMENTS

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

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

Bob Benson, the new chemical manager for allyl alcohol, made a few introductory remarks about the history of this TSD. He had recently been named the Chemical Manager as the previous chemical manager was no longer on the committee. The NAC had many previous discussions about the allyl alcohol. In previous action, the NAC had developed interim AEGL values. The TSD was returned to the NAC to respond to comments from the COT Committee.

Claudia Troxel discussed the comments from the COT (Attachment 8). The COT had comments on the derivation of values for each AEGL level. With regard to AEGL-3, the COT did not agree with the use of the adjustment factor or the modifying factor. In addition COT recommended that the value of n be derived from the lethality data. With regard to AEGL-1 and AEGL-2, the COT did not agree with the proposed values being set at the same level for all time points based on the occurrence of irritation from a 5 minute exposure. The COT recommended that the NAC consider the systemic toxicity to the liver and kidney from longer term exposure. Claudia Troxel discussed the values obtained taking into account the COT comments. After considerable discussion amongst the NAC with no clear resolution at hand because of some conflicting data, the industry observer (Dr. Marcy Banton, Lyondell Chemical) stated that her company was the sole US manufacturer of allyl alcohol and that she would ask Lyondell Chemical to conduct additional studies to resolve some of the conflicting data. The NAC enthusiastically accepted the offer and deferred action on the chemical until Dr. Banton has a decision about additional testing.

Carbon Disulfide (CAS No. 75-15-0)

Staff Scientist: Jens-Uwe Voss, Chemrisk, Germany
Chemical Manager: George Woodall, U.S. EPA

Chemical manager George Woodall reviewed the COT comments on carbon disulfide (Attachment 9). The COT agreed with the AEGL-2 and AEGL-3 values and recommended no changes. The COT commented that the discussion of sensitive subgroups should be expanded in the TSD and that the UF of 10 should be reduced to 3. Persons consuming alcohol are not a sensitive subpopulation, and an uncertainty factor of 3 should be sufficient to protect atypical metabolizers. After deliberation, a motion was made by John Hinz and seconded by Bob Benson to reduce the UF from 10 to 3 and to accept AEGL-1 values of 17 ppm for 10- and 30-min, 13 ppm for 1-hr, 8.4 ppm for 4-hr, and 6.7 ppm for 8-hr. The point-of-departure (increase in blood acetaldehyde in humans with moderate intake of alcohol) and time scaling remain unchanged. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix K).

AEGL-41

| Summary of AEGL-1 Values for Carbon Disulfide | | | | | | |
|---|-----------|-----------|--------|---------|---------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 17 ppm | 17 ppm | 13 ppm | 8.4 ppm | 6.7 ppm | Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al., 1976) |

Phosphorus Trichloride (CAS No. 7719-12-2)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Tom Hornshaw, Illinois

Bob Young reviewed the data set for phosphorus trichloride (Attachment 10) and explained that even though AEGL-1 values were based on a NOAEL for irritation in rats (3.4 ppm, 6 hr/day, 5 days/week for 4 weeks), the values had been scaled across time. In order to be consistent with the SOP, these AEGL-1 values should be held constant across time. A motion was made by Bob Benson and seconded by Ernest Falke to adopt AEGL-1 values of 0.34 ppm for all time periods. The point-of-departure and uncertainty factor of 10 remain unchanged. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix L).

| Summary of AEGL-1 Values for Phosphorus Trichloride | | | | | | |
|---|-----------|-----------|----------|----------|----------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 0.34 ppm | 0.34 ppm | 0.34 ppm | 0.34 ppm | 0.34 ppm | NOAEL for irritation in rats exposed to 3.4 ppm, 6 hr/day, 5 days/week for 4 weeks (Hazleton, 1983) |

Sulfur Dioxide (CAS No. 7446-09-5)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Woodall, U.S. EPA

The COT subcommittee commented that the AEGL-1 and AEGL-2 values for sulfur dioxide were appropriate. However, the AEGL-3 values were too high, especially at the 10-min, 30-min, and 1-hr time points.

AEGL-41

The interim AEGL-3 values (42 ppm for 10-min, 32 ppm for 30-min, 27 ppm for 1-hr, 19 ppm for 4-hr, and 16 ppm for 8-hr) were based on a rat 4-hr BMCL₀₅ of 573 ppm (Cohen et al, 1973) (Attachment 11). An uncertainty factor of 10 was applied for intraspecies extrapolation due to the wide variability in response to SO₂ exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability. Data were not sufficient to ascertain whether a maximal response to SO₂ for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling was utilized in the derivation of AEGL-3 values. The 4-hour experimental value was scaled to the 10- and 30-minute, and 1-, and 8-hour time points, using $c^4 \times t = k$.

The COT suggested using the concentration causing no deaths and a moderate Sraw response in guinea pigs (200 ppm for 1 hour) (Amdur, 1959) as the point-of departure for AEGL-3 values. An interspecies uncertainty factor of 10 would be applied because data suggest that the guinea pig is approximately 10-times less sensitive than an asthmatic human. An intraspecies uncertainty factor of 1 would be applied because the interspecies UF of 10 already accounts for extrapolation to a sensitive human subpopulation (asthmatics). Because role of exposure duration to the magnitude of SO₂-induced bronchoconstriction in asthmatics appears to decrease with extended exposure and data suggest that a major portion of the SO₂-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure, AEGL-3 values for SO₂ will be held constant across all time points. This approach yields values of 20 ppm at all time points.

After much deliberation, it was the consensus of the NAC that the decrease in airway resistance was not an appropriate endpoint for AEGL-3. However the NAC also recognized that because asthmatics are highly sensitive to sulfur dioxide for short time periods, time scaling may not be appropriate.

A motion was made by George Rodgers and seconded by Henry Anderson to retain the point-of-departure (rat 4-hr BMCL₀₅) and uncertainty factors (Intraspecies = 10, Interspecies = 3) as in the interim TSD. However, because data are not sufficient to ascertain whether a maximal response to SO₂ for a lethal endpoint is obtained within 10 minutes, time scaling will be utilized in the derivation of AEGL-3 values. Data were unavailable for an empirical derivation of *n* for sulfur dioxide. Therefore, an *n* of 3 was applied to extrapolate to the 1-hour time period, and *n* of 1 was used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health. The 1-hour AEGL-3 value was also adopted as 10-minute and 30-minute values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods. The motion passed (YES 17; NO: 1; ABSTAIN: 1) (Appendix M).

| Summary of AEGL-3 Values for Sulfur Dioxide | | | | | | |
|---|-----------|-----------|--------|--------|---------|--|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 30 ppm | 30 ppm | 30 ppm | 19 ppm | 9.6 ppm | 4-hr BMCL ₀₅ in rats (Cohen et al., 1973) |

AEGL-41

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

Staff Scientist: Claudia Troxel, CMTox

Chemical Manager: George Woodall, U.S. EPA

N, N-Dimethylformamide will be postponed to a future NAC meeting due to outstanding issues.

REVIEW of PRIORITY CHEMICALS

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

Staff Scientist: Carol Wood, ORNL

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

Carol Wood summarized the data in the TSD (Attachment 12). Proposed AEGL-1 values (27 ppm for 10- and 30-min, 21 ppm for 1-hr, 13 ppm for 4-hr, and 6.7 ppm for 8-hr) were based on an increase in motor activity and no-effect-level for asymptomatic non-clinical effects in rats exposed to 400 ppm for 4 hours (Molnar et al., 1986). Time scaling was accomplished using the default values of $n = 1$ or $n = 3$; and an interspecies UF of 3 was proposed because clinical signs and systemic effects were consistent between species. An intraspecies UF of 10 was proposed because the mechanism of systemic toxicity is unknown. Proposed AEGL-2 values (38 ppm for 10- and 30-min, 30 ppm for 1-hr, 19 ppm for 4-hr, and 13 ppm for 8-hr) were based on decreased weight gain in the absence of clinical signs in weanling rats exposed to 500 ppm for 6 hours (Stump, 2003). Uncertainty factor application and time scaling were as described for AEGL-1. Proposed AEGL-3 values (76 ppm for 10- and 30-min, 61 ppm for 1-hr, 38 ppm for 4-hr, and 25 ppm for 8-hr) were based on an approximate threshold for death in weanling rats (Stump, 2003). Uncertainty factor application and time scaling were as described for AEGL-1. Carol then discussed the possibility of using PBPK modeling to derive AEGL values for ethyl benzene (Attachment 13). Paul Tobin noted that there is a need to reference the Xylene TSD, AEGL values and animal test data, since commercial Xylene contains a significant percentage of Ethyl benzene and the AEGLs should be consistent with both compounds. After discussion, the NAC decided to defer ethyl benzene until the PBPK modeling data become available. Dr. Marcy Banton, an industry observer from Lyondell Chemical, offered assistance with the PBPK effort.

Carbonyl Fluoride (CAS No. 353-50-4)

AEGL-41

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

Sylvia Talmage reviewed the database for carbonyl fluoride (Attachment 14); no draft TSD was presented. However, input from the NAC was requested as how to proceed with the limited and conflicting data set. The main issue focuses on whether inhaled carbonyl fluoride hydrolyzes to carbon dioxide and two moles of hydrogen fluoride in the moist respiratory tract, or does some carbonyl fluoride penetrate into the lungs. If hydrolysis is essentially complete, then carbonyl fluoride AEGL values should be one-half the HF AEGL values; however, this may not be the case. The NAC suggested searching for chemical modeling data to determine the hydrolysis rate and also determine if phosgene data might be useful. This chemical will be discussed at a future meeting.

Methacrylaldehyde (CAS No.78-85-3)

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

Tom Marshall presented an overview of the TSD for methacrylaldehyde and the derivation of the draft AEGL values (Attachment 15). Proposed AEGL-1 values for 10-min, 30-min, and 1-hr (0.10 ppm) were based on a NOAEL for eye irritation in healthy humans (0.3 ppm for 20 min); whereas the proposed 4- and 8-hr AEGL-1 values (0.07 ppm) were based on a NOAEL for increased blink frequency in healthy humans (0.2 ppm for 20 min) (Nojgaard et al., 2005). An intraspecies UF of 3 was proposed because the mechanism is direct contact irritation. Proposed AEGL-2 values (2.8 ppm for 10- and 30-min, 2.2 ppm for 1-hr, 1.4 ppm for 4-hr, and 0.8 ppm for 8-hr) were derived by dividing the AEGL-3 values by 3; this approach was supported by a steep concentration-response curve. Proposed AEGL-3 values (8.3 ppm for 10- and 30-min, 6.6 ppm for 1-hr, 4.2 ppm for 4-hr, and 2.1 ppm for 8-hr) were based on an estimated 4-hr lethality threshold in rats ($\frac{1}{3}$ the LC_{50} of 125 ppm = 41.7 ppm) (Carpenter et al., 1949). Uncertainty factors of 3 each were proposed for inter- and intraspecies extrapolation because the mechanism of toxicity is direct acting irritation. Time scaling was accomplished using the default values of $n=1$ or $n=3$. Discussion of the AEGL-1 values focused on whether to use the subjective (NOAEL for irritation) or objective (blink frequency) as the point-of-departure. A motion was made by Marc Ruijten and seconded by Dieter Heinz to adopt an AEGL-1 value of 0.2 ppm for all time points. The point-of-departure is the increase in blink frequency in healthy human subjects exposed to 0.2 ppm for 20 minutes. No uncertainty factor was applied because the POD is below effects defined by AEGL-1. The motion passed (YES 14; NO: 0; ABSTAIN: 4) (Appendix N). Concern was expressed regarding the Carpenter et al. (1949) data (proposed as the POD for AEGL-3) because concentrations were not measured. A motion was made by Ernest Falke and seconded by Marc Baril to accept AEGL-3 values of 5.9 ppm for 10- and 30-min, 4.7 ppm for 1-hr, 2.9 ppm for 4-hr, and 1.9 ppm for 8-hr. The POD is $\frac{1}{3}$ of the 90% lethal level

AEGL-41

in rats exposed to 77 ppm for 6 hours ($\frac{1}{3} \times 77 \text{ ppm} = 25.7 \text{ ppm}$) (Coombs et al., 1992). This POD is supported by a repeated-exposure study showing no lethality at 19 ppm. Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation because the mechanism of toxicity is direct acting irritation. Time scaling was accomplished using the default values of $n=1$ or $n=3$. The motion passed (YES 17; NO: 0; ABSTAIN: 1) (Appendix N). A motion was then made by Marc Ruijten and seconded by Bob Benson to accept AEGL-2 values of 3.5 ppm for 10- and 30-min, 2.8 ppm for 1-hr, 1.8 ppm for 4-hr, and 1.1 ppm for 8-hr based on signs of irritation noted on the first day of exposure in rats repeatedly exposed to 15.3 ppm, 6 hr/day for 4 weeks. The use of a repeated exposure study was warranted because the only other alternative was to divide AEGL-3 values by 3. The derived AEGL-2 values are slightly higher than one-third the AEGL-3 values and are supported by comparison with the acrolein values. The motion passed (YES 18; NO: 0; ABSTAIN: 1) (Appendix N).

| Summary of AEGL Values for Methacrylaldehyde | | | | | | |
|--|-----------|-----------|----------|----------|----------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 0.20 ppm | 0.20 ppm | 0.20 ppm | 0.20 ppm | 0.20 ppm | NOAEL for increased blink frequency in humans (Nojgaard et al., 2005) |
| AEGL-2 | 3.5 ppm | 3.5 ppm | 2.8 ppm | 1.8 ppm | 1.1 ppm | Irritation in rats (Coombs et al. 1992) |
| AEGL-3 | 5.9 ppm | 5.9 ppm | 4.7 ppm | 2.9 ppm | 1.9 ppm | One-third 90% Rat lethality level (Coombs et al. 1994) |

Methyl Vinyl Ketone (CAS No. 98-94-4)

Staff Scientist: Tom Marshall, ORNL
 Chemical Manager: Jim Holler, ATSDR

Tom Marshall presented a summary of the available data and an overview of the development of proposed AEGL value for Methyl Vinyl Ketone (MVK) (Attachment 16). Proposed AEGL-1 values (0.05 ppm for all time points) were based on a NOAEL for nasal cavity lesions in rats and mice exposed to 0.5 ppm MVK, 6 hours/day, 5 days/week for 12 exposures (Morgan et al., 2000). Uncertainty factors of 3 each were proposed for inter- and intraspecies variability because MVK is a direct-acting irritant. Values were held constant at all time points. Proposed AEGL-2 values (0.66 ppm for 10-min, 0.46 ppm for 30-min, 0.36 ppm for 1-hr, 0.23 ppm for 4-hr, and 0.15 ppm for 8-hr) were based on a NOAEL for lung lesions (nasal cavity necrosis was present) in rats and mice exposed to 2 ppm MVK 6 hours/day, 5 days/week for 12 exposures (Morgan et al., 2000). Inter- and AEGL-41

intraspecies uncertainty factors of 3 each were proposed because the mechanism of action is irritation. Time scaling was performed using the $C^n \times t = k$ equation, where the values of n were the defaults of 1 or 3. Time scaling to the 10-minute value was considered appropriate because the POD was from a repeated-exposure study. Proposed AEGL-3 values (1.3 ppm for 10-min, 0.92 ppm for 30-min, 0.73 ppm for 1-hr, 0.46 ppm for 4-hr, and 0.30 ppm for 8-hr) were based on rat and mouse lethality data. There were no deaths in rats or mice exposed to 4 ppm for 12 days (Morgan et al., 2000), and there was 20% mortality in rats after 8 days of exposure to 3.9 ppm (Eastman Kodak, 1992). Inter- and intraspecies uncertainty factors of 3 each were proposed because the mechanism of action is irritation. Time scaling was performed using the $C^n \times t = k$ equation, where the values of n were the defaults of 1 or 3. Time scaling to the 10-minute value was considered appropriate because the POD was from a repeated-exposure study. A motion was made by Steve Barbee and seconded by Calvin Willhite to accept an AEGL-1 value of 0.17 ppm at all time points. The POD was as proposed. A UF of 3 will be applied for intraspecies variability; however, no interspecies uncertainty factor is considered necessary since similar NOAELs were obtained in multiple species (rat, mouse, guinea pig, rabbit) in two separate studies. The motion passed (YES: 15; NO: 1; ABSTAIN: 3) (APPENDIX O). A motion was made by Richard Niemeier and seconded by John Hinz to accept AEGL-2 values of 1.5 ppm, 1.5 ppm, 1.2 ppm, 0.76 ppm, and 0.50 ppm for 10 min, 30 min, 1, 4, and 8 hrs, respectively. The POD is as proposed, and UF application is as for AEGL-1. Time scaling uses the default n values of 1 or 3; and the 30-min value is adopted as the 10-min value. The motion passed (YES: 18; NO: 0; ABSTAIN: 1) (APPENDIX O). A motion was made by Calvin Willhite and seconded by Susan Ripple to accept AEGL-3 values of 3.1 ppm for 10- and 30-min, 2.4 ppm for 1-hr, 1.5 ppm for 4-hr, and 1.0 ppm for 8-hr. The POD is as proposed, UF application is as for AEGL-1 and AEGL-2 values and time scaling is consistent with the AEGL-2 approach. The motion passed (YES: 19; NO: 0; ABSTAIN: 0) (APPENDIX O).

| Summary of AEGL Values for Methyl Vinyl Ketone | | | | | | |
|--|-----------|-----------|----------|----------|----------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 0.17 ppm | 0.17 ppm | 0.17 ppm | 0.17 ppm | 0.17 ppm | NOAEL for respiratory tract irritation (Morgan et al. 2000) |
| AEGL-2 | 1.5 ppm | 1.5 ppm | 1.2 ppm | 0.76 ppm | 0.50 ppm | LOAEL for respiratory tract irritation (Morgan et al. 2000) |
| AEGL-3 | 3.1 ppm | 3.1 ppm | 2.4 ppm | 1.5 ppm | 1.0 ppm | Lethality at 4 ppm (Eastman Kodak 1992; Morgan et al. 2000) |

AEGL-41

Mercury Vapor (CAS No. 7439-97-6)

Staff Scientist: Sylvia Talmage, ORNL

Chemical Manager: Marquee King, U.S. EPA

An overview of the available data and the derivation of draft AEGL values was provided by Sylvia Talmage (Attachment 17). AEGL-1 values were not recommended because mercury has no odor or warning properties. Proposed AEGL-2 values (6.1 mg/m³ for 10-min, 4.2 mg/m³ for 30-min, 3.4 mg/m³ for 1-hr, 1.3 mg/m³ for 4-hr, and 0.7 mg/m³ for 8-hr) were based on the absence of lesions in pregnant rats exposed to 8 mg/m³ for 2 hours (Morgan et al., 2001). An interspecies UF of 1 was proposed due to greater lung uptake and deposition in rodents because of higher respiratory rate and cardiac output, and incompatibility with monitoring data if a higher UF is applied. For example, reviews of past workplace exposure show that concentrations in the range of 0.4-2 mg/m³ in industry have resulted in symptoms of mercury poisoning only after chronic exposure, and concentrations of 1.0-5.0 mg/m³ were not unusual in mercury mining operations in the past (AIHA 2006). An intraspecies UF of 3 was proposed because infants are more susceptible than adults, but there is no evidence that the difference is greater than 3-fold. Time scaling used default n values of 1 or 3. Proposed AEGL-3 values (16 mg/m³ for 10-min, 11 mg/m³ for 30-min, 8.9 mg/m³ for 1-hr, 2.2 mg/m³ for 4-hr, and 2.2 mg/m³ for 8-hr) were based on no clinical signs in rats exposed to 26.7 mg/m³ for 1 hour; extending the exposure for one more hour resulted in 20/32 deaths (Livardjani et al., 1991). Therefore, the POD was considered an estimate of a lethality threshold. Uncertainty factors and time scaling were proposed as for AEGL-2 except that the 8-hour AEGL-3 was set equal to the 4-hour value because time scaling resulted in a value below occupational exposures. Discussion focused on the susceptibility of the fetus and whether the proposed interspecies UF of 3 is sufficient to protect the fetus. Calvin Willhite stated that summary reports suggest that for compounds known to be developmental toxicants (such as mercury) the UF of 3 is justified; however, definitive data are not available. Ernest Falke suggested using the reconstruction studies to support the UF of 3, and Henry Anderson pointed out that for the fetus, an acute exposure is actually a chronic exposure because the mercury accumulates. A motion was then made by George Woodall and seconded by Bob Benson to adopt AEGL-3 values as proposed, supporting the UF of 3 with the human reconstruction study (16 mg/m³ for 2 hr resulted in severe health effects, but no mortality). More support for the increased rate of uptake in the rodent should also be included. The motion passed (YES: 12; NO: 4; ABSTAIN: 4) (APPENDIX P). A motion was then made by Bob Benson and seconded by Ernest Falke to adopt AEGL-2 values of 3.1 mg/m³ for 10-min, 2.1 mg/m³ for 30-min, 1.7 mg/m³ for 1-hr, 0.67 mg/m³ for 4-hr, and 0.33 mg/m³ for 8-hr based on no fetal effects in rats exposed to 4 mg/m³ for 2 hours/day for 10 days (Morgan et al., 2001). The 4 mg/m³ was selected as the POD because the proposed 8 mg/m³ is equivalent to 1/3 the LC₅₀ (7-8 mg/m³). Uncertainty factor application and time scaling were as proposed. The motion passed (YES: 11; NO: 3; ABSTAIN: 5) (APPENDIX P). A motion was then made by Ernest Falke and seconded by Jim Holler to not recommend AEGL-1 values. The motion passed unanimously by a show of hands (Appendix P).

AEGL-41

| Summary of AEGL Values for Mercury Vapor | | | | | | |
|--|-----------------------|-----------------------|-----------------------|------------------------|------------------------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | NR | NR | NR | NR | NR | Lack of data on irritation effects |
| AEGL-2 | 3.1 mg/m ³ | 2.1 mg/m ³ | 1.7 mg/m ³ | 0.67 mg/m ³ | 0.33 mg/m ³ | No fetal effects in rats (Morgan et al., 2001) |
| AEGL-3 | 16 mg/m ³ | 11 mg/m ³ | 8.9 mg/m ³ | 2.2 mg/m ³ | 2.2 mg/m ³ | Estimated lethality threshold in rats (Livardjani et al., 1991) |

Propargyl Alcohol (CAS No. 107-19-7)

Staff Scientist: Bob Young, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Bob Young reviewed the data set for propargyl alcohol (Attachment 18). Proposed AEGL-1 values (2.5 ppm at all time points) were based on no effects on olfactory or respiratory epithelium following exposure of male mice at 25.3 ppm 6 hrs/day for up to 9 days (Zissu, 1995). Support was provided by a study from BASF (1992) showing no effects in rats exposed to 9.8 ppm for ten 6-hr exposures, and metaplasia of the olfactory mucosa at 50 ppm. An interspecies UF of 3 was proposed because of a similar exposure-response profile among several species, and an intraspecies UF of 3 was applied because effects are a result of direct-acting irritation and because the POD is based on a multiple-exposure regimen. Proposed AEGL-2 values (20 ppm for 10- and 30-min, 16 ppm for 1-hr, 10 ppm for 4-hr, and 6.6 ppm for 8-hr) were based on histological changes in respiratory tract epithelium of male mice exposed to 88 ppm, 6 hr/day for 4 days (Zissu, 1995). Support was provided by a study from BASF (1992) showing metaplasia of the olfactory mucosa but no clinical signs at 50 ppm. Uncertainty factors were proposed as for AEGL-1 values and time scaling used default n values of 1 or 3. Proposed AEGL-3 values (130 ppm for 10-min, 93 ppm for 30-min, 74 ppm for 1-hr, 29 ppm for 4-hr, and 15 ppm for 8-hr) were based on a 2-hr BMCL₀₅ of 584 ppm in mice (Stasenkova and Kochetkova, 1966). Uncertainty factor application and time scaling are as proposed for AEGL-2. After a short discussion, a motion was made by Marc Ruijten and seconded by Richard Niemeier to accept AEGL-3 values as proposed. The motion passed (YES: 16; NO: 0; ABSTAIN: 1)

AEGL-41

(APPENDIX Q). A motion was made by Marc Ruijten and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 16; NO: 0; ABSTAIN: 1) (APPENDIX Q). Finally, a motion was made by Susan Ripple and seconded by Dieter Heinz to accept AEGL-1 values as proposed. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (APPENDIX Q).

| Summary of AEGL Values for Propargyl Alcohol | | | | | | |
|--|-----------|-----------|---------|---------|---------|--|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 2.5 ppm | 2.5 ppm | 2.5 ppm | 2.5 ppm | 2.5 ppm | NOAEL for respiratory tract histopathology in mice (Zissu, 195) |
| AEGL-2 | 20 ppm | 20 ppm | 16 ppm | 10 ppm | 6.6 ppm | Olfactory and respiratory epithelial lesions in mice (Zissu, 1995) |
| AEGL-3 | 130 ppm | 93 ppm | 74 ppm | 29 ppm | 15 ppm | 2-hr BMCL ₀₅ in mice (Stasenkova and Kochetkova, 1966) |

Selenium Hexafluoride (CAS No. 7783-79-1)

Staff Scientist: Cheryl Bast, ORNL

Chemical Manager: George Rusch, Honeywell

Cheryl Bast reviewed the data set for selenium hexafluoride (Attachment 19). Proposed AEGL-1 values (0.067 ppm for 10- and 30-min, 0.053 ppm for 1-hr, 0.033 ppm for 4-hr, and 0.017 ppm for 8-hr) were based on a NOEL for irritation in the guinea pig, rabbit, rats, and mice (1 ppm for 4-hours) (Kimmerle, 1960). Interspecies and intraspecies uncertainty factors of 3 each were proposed because selenium hexafluoride is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. Also, the limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride, further supporting the interspecies UF of 3. A modifying factor of 3 was also proposed to account for potential enzymatic effects of the selenium moiety and the sparse database. Time scaling utilized the default n values of 1 and 3. Although AEGL-1 values might normally be held constant across all time points because minor irritation does not vary over time, time scaling was proposed for selenium hexafluoride AEGL-1 values to account for any potential enzymatic effects resulting from the selenium moiety. In the absence of empirical data, the proposed AEGL-3 values were divided by 3 to obtain proposed AEGL-2 values (0.11 ppm for 10- and 30-min, 0.087 ppm for 1-hr, 0.057 ppm for 4-hr, and 0.083 ppm for 8-hr) for selenium hexafluoride. This approach is AEGL-41

justified based on a steep concentration response curve (no effects in rabbit, guinea pig, rat, or mouse for 4-hour exposures at 1 ppm, difficulty breathing and pulmonary edema, but no mortality at 5 ppm, and 100% mortality at 10 ppm) (Kimmerle, 1960). Proposed AEGL-3 values (0.33 ppm for 10- and 30-min, 0.26 ppm for 1-hr, 0.17 ppm for 4-hr, and 0.083 ppm for 8-hr) were based on the highest concentration causing no mortality in the guinea pig, rabbit, rats, and mice (5 ppm for 4-hours) (Kimmerle, 1960). Time scaling and uncertainty factor application were as proposed for AEGL-1 values. After a discussion focusing on whether enough data existed to derive AEGL values for selenium hexafluoride, a motion was made by Marc Baril and seconded by Richard Niemeier to adopt AEGL-3 values as proposed except that the interspecies UF will be reduced from 3 to 1 because available data show no interspecies differences and the MF will increase from 3 to 10 because of the sparse data base and potential selenium effects (the intraspecies UF and resulting AEGL values remain the same). The motion passed (YES: 14; NO: 3; ABSTAIN: 0) (APPENDIX R). A motion was then made by Richard Niemeier and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 14; NO: 3; ABSTAIN: 0) (APPENDIX R). A motion was then made by Dieter Heinz and seconded by Susan Ripple to accept AEGL-1 values as proposed except that the interspecies UF will be reduced from 3 to 1 because available data show no interspecies differences and the MF will increase from 3 to 10 because of the sparse data base and potential selenium effects (the intraspecies UF and resulting AEGL values remain the same). The motion passed (YES: 13; NO: 4; ABSTAIN: 0) (APPENDIX R).

| Summary of AEGL Values for Selenium Hexafluoride | | | | | | |
|--|-----------|-----------|-----------|-----------|-----------|---|
| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
| AEGL-1 | 0.067 ppm | 0.067 ppm | 0.053 ppm | 0.033 ppm | 0.017 ppm | NOEL for irritation in rabbit, guinea pig, rats, and mice (Kimmerle, 1960) |
| AEGL-2 | 0.11 ppm | 0.11 ppm | 0.087 ppm | 0.057 ppm | 0.028 ppm | One-third of the AEGL-3 values |
| AEGL-3 | 0.33 ppm | 0.33 ppm | 0.26 ppm | 0.17 ppm | 0.083 ppm | Highest concentration causing no mortality in rabbit, guinea pig, rats, and mice (Kimmerle, 1960) |

Oxygen Difluoride (CAS No. 7783-41-7)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

The discussion of this chemical was postponed pending evaluation of new monkey data.

AEGL-41

Thionyl Chloride (CAS No. 7719-09-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Steve Barbee, Arch Chemical

Steve Barbee reviewed the data set for thionyl chloride (Attachment 20). Data are not available from human or animal studies to derive AEGL-1 values. Therefore, proposed AEGL-1 values are not recommended. Proposed AEGL-2 values (4.3 ppm for 10-min, 3.0 ppm for 30-min, 2.4 ppm for 1-hr, 0.59 ppm for 4-hr, and 0.30 ppm for 8-hr) were based on swollen noses and dyspnea, but no irreversible or incapacitating effects in rats exposed to 71 ppm thionyl chloride for one hour (Pauluhn 1987). A total uncertainty factor of 30 was proposed. A similar mechanism of action would be expected across species, therefore, an uncertainty factor of 3 was proposed for interspecies variability while a factor of 10 was proposed for intraspecies variability to account for sensitive populations. Thionyl chloride hydrolyzes into sulfur dioxide and hydrogen chloride. Asthmatics are more sensitive than healthy people to the effects of sulfur dioxide. Time scaling used default n values of 1 or 3. The proposed AEGL-3 values (25 ppm for 10-min, 17 ppm for 30-min, 14 ppm for 1-hr, 3.4 ppm for 4-hr, and 1.7 ppm for 8-hr) were based upon the highest concentration causing no lethality in rats exposed to thionyl chloride for one hour (Pauluhn 1987; Nachreiner 1993). A one hour exposure to 593 ppm produced 58% mortality (Nachreiner 1993), the next highest experimental concentration at which no mortality was observed (407 ppm, Pauluhn 1987) was used as the point of departure. This concentration is only slightly greater than the lethality threshold (371 ppm) reported in Nachreiner (1993). The same uncertainty factors and rationale and time scaling used for AEGL-2 were applied to AEGL-3 calculations. Discussion focused on why the HCl AEGL values are much higher than the proposed thionyl chloride values. The fact that HCl is well-scrubbed in the respiratory tract and thionyl chloride is not as well scrubbed may account for the difference. A statement to this effect should be added to the TSD. Another point of discussion involved the use of the highest experimental concentration causing no death, rather than the calculated $BMCL_{05}$, as the POD for AEGL-3. The experimental concentration was used because the calculated value provided a bad "model fit" (p value is 0.002 and should be >0.1). A motion was made by Richard Thomas and seconded by Ernest Falke to accept AEGL-1 values as proposed. The motion passed unanimously by a show of hands (Appendix S). A motion was then made by Marc Baril and seconded by Henry Anderson to accept AEGL-3 values as proposed. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX S). Finally, a motion was made by Susan Ripple and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX S).

| Summary of AEGL Values for Thionyl 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 | 4.3 ppm | 3.0 ppm | 2.4 ppm | 0.59 ppm | 0.30 ppm | Dyspnea (Pauluhn 1987) |
| AEGL-3 | 25 ppm | 17 ppm | 14 ppm | 3.4 ppm | 1.7 ppm | Threshold of lethality (Pauluhn 1987; Nachreiner 1993) |

GENERAL ISSUES

DFO Award: Paul Tobin was the recipient of the FACA Distinguished Designated Federal Officer Award in recognition of his work with the NAC/AEGL.

Suggestion on TSD Review Process: Calvin Willhite suggested that a “TLV Model” be used in AEGL document review to help TSDs get through the NAC and COT subcommittee more efficiently. Specifically, he suggested that the AEGL development teams meet the first half day of the meeting to discuss the TSD and presentation. George Rusch suggested that this same type of meeting could occur by teleconference prior to the meeting. However, for NAC-42, a pilot break-out session could be held if the teleconferences did not work.

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-42: March 20-22, 2007, Irvine, CA

NAC/AEGL-43: June 20-22, 2007, Rotterdam, Netherlands

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

AEGL-41

LIST OF ATTACHMENTS

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

- Attachment 1. NAC/AEGL-41 Meeting Agenda
- Attachment 2. NAC/AEGL-41 Attendee List
- Attachment 3. Review of FR-09 comments for formaldehyde
- Attachment 4. Review of FR-09 comments for titanium tetrachloride
- Attachment 5. Review of FR-09 comments for benzene
- Attachment 6. Review of FR-09 comments for methacrylic acid and methyl methacrylate
- Attachment 7. Review of FR-09 comments for styrene
- Attachment 8. Review of COT comments for allyl alcohol
- Attachment 9. Review of COT comments for carbon disulfide
- Attachment 10. Review of COT comments for phosphorus trichloride
- Attachment 11. Review of COT comments for sulfur dioxide
- Attachment 12: Data analysis for ethyl benzene
- Attachment 13: PBPK modeling for ethyl benzene
- Attachment 14: Data analysis for carbonyl fluoride
- Attachment 15: Data analysis for methacrylaldehyde
- Attachment 16: Data analysis for methyl vinyl ketone
- Attachment 17: Data analysis for mercury vapor
- Attachment 18: Data analysis for propargyl alcohol
- Attachment 19: Data analysis for selenium hexafluoride
- Attachment 20: Data analysis for thionyl chloride

LIST OF APPENDICES

- Appendix A. Ballot for NAC-40 meeting summary
 - Appendix B. Final NAC-40 Meeting Highlights
 - Appendix C. Ballot for ethyl acrylate
 - Appendix D. Ballot for butyl acrylate
 - Appendix E. Ballot for formaldehyde
 - Appendix F. Ballot for titanium tetrachloride
 - Appendix G. Ballot for benzene
 - Appendix H. Ballot for methacrylic acid
 - Appendix I. Ballot for methyl methacrylate
 - Appendix J. Ballot for styrene
 - Appendix K. Ballot for carbon disulfide
 - Appendix L. Ballot for phosphorus trichloride
 - Appendix M. Ballot for sulfur dioxide
 - Appendix N. Ballot for methacrylaldehyde
 - Appendix O. Ballot for methyl vinyl ketone
 - Appendix P. Ballot for mercury vapor
 - Appendix Q. Ballot for propargyl alcohol
 - Appendix R. Ballot for selenium hexafluoride
 - Appendix S. Ballot for thionyl chloride
 - Appendix T. Committee chairman certification of minutes
- AEGL-41