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

April 14-16, 2009

Meeting-48 Highlights

Hilton- Old Town Alexandria
1867 King Street
Alexandria, VA

INTRODUCTION

Chairman George Rusch opened the meeting by calling for an introduction of all committee members and guests. George mentioned that even after 48 meetings, there is still a high level of interest in the AEGL Process. This interest is evidenced by the presence of all committee members, as well as visitors from several foreign countries.

The draft NAC/AEGL-47 meeting highlights were reviewed. George Woodall suggested including a statement indicating that he would forward the acrylonitrile TSD to NCEA/IRIS for review. Bob Benson requested corrections to the allyl alcohol summary (change nasal irritation to nasal inflammation and deleting benchmark language when referring to tenBerge probit calculations). George Rusch requested correction of the AEGL-3 vote count for dichlorvos. A motion to accept the minutes as written with the aforementioned corrections was made by Dieter Heinz (second by Gail Chapman) and passed unanimously (Appendix A). The Final NAC/AEGL-47 meeting highlights are included as Appendix B.

Marcel van Raaij announced that the OECD 403 (acute toxicity) guidelines have been revised to incorporate the c^n x t protocol.

Susan Ripple pointed out that some organizations may assign specific risk values to AEGL values (AEGL values are being run through Probit analysis). During the discussion of whether AEGL values should be used beyond Risk Management Planning (RMP) as they are originally intended for such assessments as probit analyses, there was clear consensus in the NAC AEGL Committee regarding the use of the actual AEGL values. The NAC/AEGL is not in a position to tell other risk assessors how they may, or may not, use these values. However, because the AEGL-3 value includes as part of its definition terminology the "threshold for lethality above which we would expect to see some lethality in community members", some non-toxicologist assessors may arbitrarily assume the AEGL-3 is the Lethal Concentration 0% (LC_0) for humans.

There is a clear need to make sure that these assessors understand that there is no attempt to quantify the risk to humans in terms of traditional risk assessment targets (e.g. 1 x 10^{-6} or 1 in 1000, etc.) but rather that the AEGL-3 value is a strictly health-based number based on the toxicology data available. Although these assessors may choose to make various assumptions on their part for risk management planning purposes, they should clearly understand that their assumptions for risk may NOT be assigned to the AEGL values or the definitions of those values. Clearly, AEGLs are strictly health-based estimates of thresholds for the target endpoint.

The highlights of the NAC/AEGL-48 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-48 Agenda.

CHEMICAL LIST

Ernest Falke announced that the NAC/AEGL will essentially be finished with the chemical list at NAC-49 (September, 2009); it is likely that no new chemicals will be addressed after September, 2009. Unleaded gasoline and carbon dioxide, not on the original list, will be addressed in September, 2009. The EPA management has directed that emphasis shift to finalization and publication of TSDs through the COT process.

CHEMICAL REVISITS/STATUS UPDATES

No Data Chemicals

Cheryl Bast (ORNL) provided a status update for Diacetylmorphine, Fluoroacetate salts, Methyl fluoroacetate, Methoxyethylmercuric acetate, Monofluoroacetic acid, Paraquat, Phencyclidine, Sodium fluoroacetate, Tetraethylpyrophosphate, Tetramethylenedisulfotetramine, and Tungsten hexafluoride. These chemicals have no data and will be placed in holding status. Susan Ripple made a motion (seconded by Dieter Heinz) to validate that these chemicals have insufficient data to derive AEGL values. The motion passed unanimously by a show of hands (Appendix C).

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

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Alan Becker, Florida A & M Univ.

A status update was provided by Sylvia Talmage. The PBPK modeling results for methyl iodide will be published in an upcoming issue of Inhalation Toxicology. Methyl iodide will be addressed at NAC-49 (September, 2009).

Arsenic Pentoxide (CAS No. 1303-28-2)
Arsenic Trichloride (CAS No. 7784-34-1)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Roberta Grant, Texas

Bob Young discussed a possible approach for derivation of AEGL values for arsenic pentoxide and arsenic trichloride (Attachment 3). Chemical-specific data are not available for derivation of AEGL values; therefore, an elemental equivalence approach was discussed. After a discussion of the assumptions inherent in this approach, a motion was made by Roberta Grant and seconded by Susan Ripple to place arsenic pentoxide and arsenic trioxide in holding status due to insufficient data. The motion passed unanimously by a show of hands (Appendix D).

Ricin (CAS No. 9009-86-3)

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

Bob Young discussed new ricin data (Gomez et al., 2009) presented in a poster session at the Society of Toxicology meeting in March, 2009 (Attachment 4). The new data, from acute inhalation toxicity studies in both rats and mice, suggest that the currently proposed ricin AEGL values (key study is Griffiths et al, 1995) may be too high. After a discussion of the new data, a motion was made by John Hinz and seconded by George Woodall to reconsider the ricin values at a future AEGL meeting and place the ricin TSD in holding status. The motion passed unanimously by a show of hands (Appendix E). Bob Young will contact the authors of the Gomez poster to obtain a study report. An attempt will also be made to determine why there is an apparent difference in inhalation toxicity between the Gomez and Griffiths studies.

REVIEW of PRIORITY CHEMICALS

Selected Cyanide Salts
Sodium Cyanide (CAS No. 143-33-9)

Potassium Cyanide (CAS No. 151-50-8)
Calcium Cyanide (CAS No.592-01-8)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ralph Gingell, Shell Health Services

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for the selected cyanide salts (Attachment 5). In the absence of appropriate chemical-specific data for the title cyanides, the use of AEGL-1, AEGL-2, and AEGL-3 values for hydrogen cyanide was proposed to obtain AEGL-1, AEGL-2, and AEGL-3 values, respectively for the title cyanide salts. The use of hydrogen cyanide as a surrogate for the cyanide salts was deemed appropriate because qualitative (clinical signs) and quantitative (adjusted rat oral LD_{50} values) data suggest that the cyanide moiety is responsible for acute toxicity of the cyanide salts. The hydrogen cyanide AEGL values were used as target values for calculating the concentrations of cyanide salt needed to generate the hydrogen cyanide AEGL values. Calculations assumed 25 degrees C and 760 mm Hg and complete hydrolysis (one mole of NaCN and KCN will each yield one mole of HCN, and one mole of $Ca(CN)_2$ will yield two moles of HCN).

A motion was made by Richard Niemeier and seconded by Dieter Heinz to accept the AEGL-1, AEGL-2, and AEGL-3 values as proposed for sodium cyanide, potassium cyanide, and calcium cyanide. The motion passed. (Sodium Cyanide: Appendix F: 24 yes; 0 no; 0 abstain), (Potassium Cyanide: Appendix G: 24 yes; 0 no; 0 abstain), (Calcium Cyanide: Appendix H: 24 yes; 0 no; 1 abstain). Calvin Willhite will provide material to revise and expand the mechanism of action section of the TSD.

AEGL VALUES FOR METAL CYANIDE SALTS*						
Compound	**Classification**	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
Sodium Cyanide	**AEGL-1**	5.0 mg/m^3	5.0 mg/m^3	4.0 mg/m^3	2.6 mg/m^3	2.0 mg/m^3
	AEGL-2	34 mg/m^3	20 mg/m^3	14 mg/m^3	7.0 mg/m^3	5.0 mg/m^3
	AEGL-3	54 mg/m^3	42 mg/m^3	30 mg/m^3	17 mg/m^3	13 mg/m^3
Potassium Cyanide	**AEGL-1**	6.6 mg/m^3	6.6 mg/m^3	5.3 mg/m^3	3.5 mg/m^3	2.7 mg/m^3
	AEGL-2	45 mg/m^3	27 mg/m^3	19 mg/m^3	9.3 mg/m^3	6.6 mg/m^3
	AEGL-3	72 mg/m^3	56 mg/m^3	40 mg/m^3	23 mg/m^3	18 mg/m^3
Calcium Cyanide**	**AEGL-1**	4.7 mg/m^3	4.7 mg/m^3	3.8 mg/m^3	2.4 mg/m^3	1.9 mg/m^3
	AEGL-2	32 mg/m^3	19 mg/m^3	13 mg/m^3	6.6 mg/m^3	4.7 mg/m^3
	AEGL-3	51 mg/m^3	39 mg/m^3	28 mg/m^3	16 mg/m^3	12 mg/m^3

- *These airborne concentrations will produce the equivalent AEGL values for hydrogen cyanide.
- ** Although the adjusted rat oral LC value for calcium cyanide is much greater (suggesting a less toxic compound) than would be expected on a molar basis for CN, the production of two moles of HCN was assumed per mole of calcium cyanide. This assumption will yield protective AEGL values.

Phosgene Oxime (CAS No.1794-86-1)

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

Robert Young summarized the limited data set data for phosgene oxime (Attachment 6). Draft AEGL-1 values (0.17 mg/m^3 at all time points) were based on awareness (ocular, nasal and dermal sensation) of the chemical by human volunteers exposed to 1 mg/m^3 for 10-minutes (Malatesta et al., 1983). An intra species UF of 3 was proposed because direct contact irritation is not expected to vary among individuals. A modifying factor of 2 was proposed for limited data. No time scaling was proposed (direct contact irritation). Draft AEGL-2 values (0.50 mg/m^3 at all time points) were based on unpleasant/intolerable irritation of eyes, nasal tissue, and skin in human volunteers exposed to 3 mg/m^3 for 1-minute (Malatesta et al., 1983). An intra species UF of 3 was proposed because direct contact irritation is not expected to vary among individuals. A modifying factor of 2 was proposed for limited data. No time scaling was proposed (direct contact irritation). Draft AEGL-3 values were not recommended due to insufficient data. After extensive discussion, a motion was made by Calvin Willhite and seconded by John Hinz to base AEGL-3 values on the highest nonlethal exposure (500 mg/m^3 for 30 minutes) reported by Malatesta et al. (1983) for mice, guinea pigs and rabbits. Malatesta et al. (1983) observed agitation, respiratory difficulty, and intense lacrimation in these animals during the 30-minute exposure to phosgene oxime at concentrations of 100-500 mg. The uncertainty factor for interspecies extrapolation was limited to 3 because all the of species tested responded similarly. The uncertainty factor of 3 for individual variability was considered sufficient for direct-contact damage attributed to the actions of the parent molecule. A modifying factor of 2 was applied for data deficiencies. In the absence of an empirically derived exponent (n), temporal scaling from the 30-minute experimental duration to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The motion passed. (Appendix I: 18 yes; 2 no; 4 abstain). Concern that a larger MF was warranted was expressed by those abstaining or voting no.

A motion was then made by Calvin Willhite and seconded by Marc Baril for derivation of both AEGL-1 and AEGL-2 values. AEGL-1 values were based on awareness of the chemical as determined by ocular, nasal and dermal sensations by volunteers exposed for 10 minutes to 1 mg/m^3 (Malatesta et al., 1983). This sensory perception was not considered to be disabling. The use of data obtained from exposures of informed human volunteers eliminates the animal-to-human extrapolation concerns allowing an interspecies uncertainty factor of 1. Because the initial effects of phosgene oxime appear to be the result of direct-contact with exposed tissue (eyes, nasal mucosae, skin), an uncertainty factor of 3 was considered sufficient to account for possible individual variability. Metabolism and disposition processes would not be critical in such immediate

responses. Because rigorous empirical data regarding exposure concentration-duration relationship are not available for phosgene oxime, and because more severe effects appear to occur with increasing concentration, time scaling where n =1 in the relationship $C^n \times t = k$ was applied to obtain AEGL values for time points greater that 10 minutes. A modifying factor of 2 was applied in derivation of the AEGL-1 values to account for limited information on the inhalation toxicity of phosgene oxime as well as the lack of methodologic detail in the Malatesta et al. (1983) report. AEGL-2 values were based upon the same point-of-departure (POD) used for deriving AEGL-1 values; irritation (ocular, dermal, nasal) in volunteers exposed to phosgene oxime at a concentration of 1 mg/m^3 for 10 minute (Malatesta et al., 1983). No uncertainty factor for sensitive individuals was applied with the implication that the exposure may result in effects approaching AEGL-2 severity for these individuals. This approach was considered more defensible than utilizing notable irritation reported by Malatesta et al. (1983) for volunteers exposed to 3 mg/m^3 for only 1 minute. Data from volunteers precluded application of an interspecies uncertainty factor greater than 1. As for AEGL-1 derivation, a modifying factor of 2 was applied for overall data deficiencies as well as study deficiencies. Time scaling was applied as described for AEGL-1; $C^n \times t = k$, where n=1. The motion passed. (Appendix I: 20 yes; 0 no; 4 abstain).

AEGL Values for phosgene oxime expressed as mg/m^3 [ppm]						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.17 [0.036]	0.056 [0.012]	0.028 [0.0059]	0.0069 [0.0014]	0.0035 [0.00074]	Awareness (ocular, nasal, dermal sensation) by human volunteers; 1 mg/m^3 for 10 min.; UF=1 x 3; MF=2; n=1 (Malatesta et al., 1983)
AEGL-2 (Disabling)	0.50 [0.011]	0.17 [0.036]	0.083 [0.017]	0.021 [0.0044]	0.010 [0.0021]	Unpleasant irritation (ocular, nasal, dermal) in human volunteers at 3 mg/m^3 for 1 min.; UF=1 x 1; MF=2; n=1 (Malatesta et al., 1983)
AEGL-3 (Lethality)	36 [7.6]	25 [5.3]	13 [2.7]	3.1 [0.65]	1.6 [0.34]	Highest nonlethal exposure in animals (500 mg/m^3 for 30 min.; UF= 3 x 3; MF=2; n=1 (Malatesta et al., 1983)

Perfluoroisobutylene (CAS No. 382-21-8)

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

Cheryl Bast provided a review of the available data and draft AEGL values for perfluoroisobutylene (PFIB) (Attachment 7). Data were insufficient for derivation of AEGL-1 values; therefore, draft AEGL-1 values were not recommended. In the absence of appropriate chemical-specific data, the draft AEGL-3 values were divided by 3 to derive draft AEGL-2 values for PFIB (NRC, 2001). This approach is justified by the steep concentration-response curve observed in several animal studies. No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (2/2) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968). The highest concentration causing no mortality in rats exposed to PFIB for 4-hours (0.25 ppm) was used as the point-of-departure for draft AEGL-3 values (DuPont, 1966). Clinical signs noted at this concentration included face washing, hyperemia, sneezing, hypernea, dyspnea, and decreased responsiveness. There was 100% mortality (6/6) at the next highest concentration tested (0.5 ppm). Inter- and intraspecies uncertainty factors of 3 each were applied (total 10). The interspecies UF of 3 was considered sufficient because lethality data available for several animal species suggest little interspecies variability; LC_{50} values for given exposure durations were well within a factor of 3). Reported 1-min LC_{50} values are 107 ppm for mice (Fusheng et al., 1992) and 122 ppm for rats (Smith et al., 1982); 10-minute values are 11.8 ppm for mice (Bide et al., 2000) and 17 ppm for rats (Smith et al., 1982); 15 minute values are 6.1 ppm for mice and 6.7 ppm for rats (Karpov, 1977); and reported 2-hour values are 0.98 ppm (Paulet and Bernard, 1968) and 1.6 ppm for mice (Karpov, 1977), 1.05 ppm for rats and guinea pigs (Paulet and Bernard, 1968), and 1.20 ppm for rabbits (Karpov, 1977). The intraspecies UF of 3 was supported by the steep concentration-response curve for PFIB (described above for AEGL-2), implying limited intraspecies variability. Values were scaled across time using the $C^n \times t = k$, relationship where the exponent, n, was the chemical-specific value of 1.0, derived from rat LC_{50} data ranging from 0.25 to 120 minutes.

After discussion, a motion was made by Richard Niemeier and seconded by Dieter Heinz to accept values as presented except that the interspecies uncertainty factor be reduced to 1 (total UF = 3). This UF reduction is warranted because of essentially no variability in lethality data from rats, mice, guinea pigs, and rabbits. The motion passed. (Appendix J: 23 yes; 0 no; 0 abstain).

Summary of AEGL Values for PFIB						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL–2 (Disabling)	0.67 ppm (5.5 mg/m^3)	0.22 ppm (1.8 mg/m^3)	0.11 ppm (0.90 mg/m^3)	0.028 ppm (0.23 mg/m^3)	0.014 ppm (0.11 mg/m^3)	1/3 the AEGL-3 values.
AEGL–3 (Lethal)	2.0 ppm (16 mg/m^3)	0.67 ppm (5.5 mg/m^3)	0.33 ppm (2.7 mg/m^3)	0.083 ppm (0.68 mg/m^3)	0.042 ppm (0.34 mg/m^3)	Highest concentration causing no lethality in rats (0.25 ppm; 4-hr). 100% mortality at next concentration (0.5 ppm) tested (DuPont, 1966)

Carbofuran (CAS No. 11563-66-2)

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

Carbofuran was postponed to a future NAC/AEGL meeting.

Oxamyl (CAS No. 23135-22-0)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Data on oxamyl, the first of three *N*-methyl carbamates discussed, was presented by Sylvia Talmage (Attachment 8). The *N*-methyl carbamates are neurotoxicants; uptake results in reversible inhibition of acetylcholinesterase, the enzyme responsible for the termination of the biological activity of the neurotransmitter acetylcholine at various nerve endings. All three chemicals are solids with low vapor pressures. Human oral dosing studies were available for all three *N*-methyl carbamates. The data base for oxamyl AEGL consideration consisted of one- and 4-hour inhalation lethality studies with the rat. The chemical was inhaled as a dust or powder.

The point of departure for the AEGL-1 was a 4-hour study in which rats inhaled 4.9 or 24 mg/m^3 (U.S. EPA 2000). Slight symptoms of cholinesterase activity inhibition were observed at the 4-hour point of departure of 4.9 mg/m^3. In the absence of data describing effects consistent with the definition of an AEGL-2, the AEGL-2 values were derived by dividing the AEGL-3 values by 3. The AEGL-3 values were based on the calculated $BMCL_{05}$ of 22 mg/m^3 in a 4-hour GLP study with the rat (Kelly 2001). Initially, interspecies and intraspecies uncertainty factors of 3 and 3.48, respectively, for a total of 10 were proposed. The uncertainty factors were based on comparative cholinesterase activity inhibition following oral dosing in humans and juvenile and adult rats (U.S.

EPA 2007). The uncertainty factors from oral dosing were suggested because *N*-methyl carbamates do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation. The oxamyl-specific interspecies inhalation uncertainty factor was based on differences in modeled red blood cell values for cholinesterase activity inhibition between rats and humans following oral dosing. Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated a Food Quality Protection Act safety factor of 3.48 to protect children, the most sensitive population. The resulting values were time-scaled (C^n x t = k) from the 4-hour data point using an n value of 1.6 derived from three lethality studies involving exposure durations of 1 and 4 hours. After discussion, the Committee considered an intraspecies uncertainty factor of 10, used for the organophosphate AEGL derivations, more appropriate. The 10-minute through 8 hour exposure duration values were AEGL-1: 1.2, 0.60, 0.39, 0.16, and 0.11 mg/m^3; AEGL-2: 1.8, 0.90, 0.57, 0.24, and 0.16 mg/m^3; AEGL-3: 5.3, 2.7, 1.7, 0.73, and 0.28 mg/m^3. It was moved by John Hinz and seconded by Alan Becker to accept the values. The motion passed ((Appendix K: 20 yes; 1 no; 1 abstain).

Following acceptance of the U.S. EPA oral-dosing-based uncertainty factors for methomyl, the oxamyl motion of the previous day was rescinded. Daniel Sudakin explained that the *N*-methyl carbamates are not a substrate for the A-esterases that metabolize the organophosphates. The A-esterases show great inter-individual variation; whereas there was little variation in metabolism of carbamates in the human oral dosing studies. It was moved by John Hinz and seconded by Marc Baril to accept the AEGL values as originally presented (total uncertainty factor of 10 and time scaling with an n value of 1.6). The motion passed (Appendix L: 18 yes; 1 no; 2 abstain).

Summary of AEGL Values for Oxamyl						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	3.6 mg/m^3	1.8 mg/m^3	1.2 mg/m^3	0.49 mg/m^3	0.32 mg/m^3	Slight symptoms of cholinesterase activity inhibition – rat (U.S. EPA 2000)
AEGL–2 (Disabling)	5.3 mg/m^3	2.7 mg/m^3	1.8 mg/m^3	0.73 mg/m^3	0.47 mg/m^3	One-third of the AEGL-3 values
AEGL–3 (Lethal)	16 mg/m^3	8.2 mg/m^3	5.3 mg/m^3	2.2 mg/m^3	1.4 mg/m^3	4-hour $BMCL_{05}$ for lethality – rat (Kelly 2001)

Methomyl (CAS No. 16752-77-5)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Data on the *N*-methyl carbamate, methomyl, were presented by Sylvia Talmage (Attachment 9). All inhalation studies used the rat as the test species and all studies were 4 hours in duration. Methomyl was inhaled as a vapor, powder, or liquid aerosol. The study of Ta'naka et al. (1987) in which rats

inhaled 9.9 mg/m^3 methomyl for 4 hours was rejected as the basis for the AEGL-1 due to questionable acetylcholinesterase activity measurements. In the absence of data that met the definition of an AEGL-1, an AEGL-1 was not recommended. A study conducted by DuPont (1966) in which rats showed clinical signs of cholinesterase activity inhibition during inhalation of 44 mg/m^3 of methomyl powder was suggested as the basis for the AEGL-2. In light of the steep concentration-response curve, the Committee instead decided to derive the AEGL-2 values by dividing the AEGL-3 values by 3. The DuPont (1966) study was used as support for the AEGL-2 values. The AEGL-3 was based on the calculated 4-hour $BMCL_{05}$ of 157.3 mg/m^3 from the study of DuPont (1991). The highest concentration of 326 mg/m^3 was omitted from the calculation in order to improve the fit of the data to the concentration-response curve. The $BMCL_{05}$ was divided by interspecies and intraspecies uncertainty factors of 5 and 3.05, respectively, for a total of 15. These methomyl-specific uncertainty factors were based on oral dosing studies with methomyl (as described for oxamyl above). In the absence of time-scaling information, the 4-hour value of 10.48 mg/m^3 value (157.3/15) was time-scaled to the shorter and longer exposure durations using default uncertainty factors of 3 and 1, respectively. Because the key study was 4 hours, the 10-minute AEGL-3 was set equal to the 30-minute AEGL-3. It was moved by Dieter Heinz and seconded by John Hinz to accept the values as proposed. The motion passed (Appendix M: AEGL-1: 19 yes; 0 no; 1 abstain; AEGL-2: 16 yes; 0 no; 4; abstain; AEGL-3: 15 yes; 2 no; 3 abstain).

Summary of AEGL Values for Methomyl						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL−1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL−2 (Disabling)	7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3	One-third of the AEGL-3 values
AEGL−3 (Lethal)	21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3	4-hour $BMCL_{05}$ for lethality – rat (DuPont 1991)

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

Aldicarb (CAS No. 116-06-3)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Paul Tobin, U.S. EPA

Data on the third *N*-methyl carbamate, aldicarb, were presented by Sylvia Talmage (Attachment 10). The data base for aldicarb is relatively sparse. In the absence of data that meets the definition of an AEGL-1, an AEGL-1 was not recommended. Data that addressed the definition of an AEGL-2 were also sparse. Based on the steep concentration-response curve, the AEGL-2 values were calculated by dividing the AEGL-3 values by 3. The key study for derivation of AEGL-3 values was reported by Union Carbide Corp. (UCC 1985). Rats inhaled a liquid aerosol of aldicarb for 4 hours. Concentrations ranged from 0.82 to 46.3 mg/m^3. The calculated $BMCL_{05}$ was 0.97 mg/m^3. Interspecies and intraspecies uncertainty factors of 2 and 2, derived by U.S. EPA (2007) and based

on oral dosing as described above for oxamyl, were suggested. For consistency with the prior two *N*-methyl carbamates, the intraspecies uncertainty factor was raised to 3 for a total of 6. Time scaling utilized the default n values of 3 and 1 for shorter and longer exposure durations, respectively. Because data were available from a study of short duration (Risher et al. 1987), time-scaling included the 10-minute value. It was moved by Marcel van Raaij and seconded by George Woodall to accept the values as proposed. The motion passed (Appendix N: 18 yes; 0 no; 3 abstain).

Summary of AEGL Values for Aldicarb						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
AEGL–2 (Disabling)	0.16 mg/m^3	0.11 mg/m^3	0.087 mg/m^3	0.053 mg/m^3	0.027 mg/m^3	One-third of the AEGL-3 values
AEGL–3 (Lethal)	0.47 mg/m^3	0.32 mg/m^3	0.26 mg/m^3	0.16 mg/m^3	0.081 mg/m^3	4-hour $BMCL_{05}$ for lethality – rat (UCC 1985)

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

Following acceptance of AEGL values for all three *N*-methyl carbamates, the relationship among the AEGL-3 values at the 4-hour time point was compared to the calculated 4-hour LC_{50} values. For aldicarb, oxamyl, and methomyl, the 4-hour LC_{50} values are 3.9, 56, and 258 mg/m^3, respectively. Compared with the 4-hour AEGL-3 values of 0.16, 2.2, and 10 mg/m^3, respectively, the relationship held.

Perchloryl Fluoride (CAS No. 7616-94-6)

Staff Scientist: Dana Glass, ORNL
Chemical Manager: Glenn Leach, U.S. ACHPPM

Glenn Leach, the chemical manager, presented several scenarios for development of AEGL values (Attachment 11). Human data were not considered in deriving values because the clinical study addressed odor, and the exposure was of unknown duration. Acute studies with the dog, rat, mouse, and guinea pig (Greene et al. 1960) showed that perchloryl fluoride is a direct contact irritant as well as a systemic toxicant. Methemoglobinemia was observed in all animals exposed to high concentrations of perchloryl fluoride. A second acute study with the rat (Dost et al. 1974) was presented, but details of exposure were lacking. Both studies addressed lethal concentrations. No acute data were available for determination of AEGL-1 and AEGL-2 values. The AEGL-1 values were derived from the concentration, 24 ppm, at which dogs and rats were exposed for 6 hours/day, 5 days/week for 26 weeks. At this concentration, all animals survived, exhibited no clinical signs, no signs of irritation and the only long-term effect observed was increased fluoride deposition in the bone and urine over the course of the 26 weeks. Therefore, this may be considered a no-effect level

over an eight hour period. The POD, 24 ppm, was divided by interspecies and intraspecies uncertainty factors of 3 and 10, respectively, for a total of 30. An interspecies uncertainty factor of 3 was appropriate as lethality values among dogs, rats, and mice differed by less than a factor of 3. An intraspecies uncertainty factor of 10 was considered appropriate because infants are considerably more susceptible to methemoglobinemia than healthy adults. In the absence of time-scaling information, the 6-hour value was time-scaled to the shorter and longer exposure durations (C^n x t = k) using the default values of 3 and 1, respectively. Because of uncertainty in time-scaling from an 6-hour exposure duration to 10 minutes, the 10-minute value was set equal to the 30-minute value. Because of the steep concentration-response curve for lethality in the key study (Greene et al. 1960), AEGL-2 values were derived by dividing the AEGL-3 values by three. The committee chose a 4-hour exposure of two dogs to 224 ppm (Greene et al. 1960) as the point of departure for AEGL-3. Dogs survived the next highest exposure of 425 ppm, but this concentration was above the 4-hour LC_{50} of 385 ppm for the rat. The 4-hour 224 ppm concentration was divided by interspecies and intraspecies uncertainty factors of 3 and 10, respectively, for a total of 30. The interspecies uncertainty factor of 3 was justified based on the fact that LC_{50} concentrations for the dog, rat, and mouse in the key study were within a 3-fold factor of each other. The intraspecies uncertainty factor of 10 was used because the fetal hemoglobin of infants is considerably more sensitive to oxidation to methemoglobin than the hemoglobin of adults. In the absence of time-scaling information, the 4-hour value of 7.5 ppm was time-scaled to the shorter and longer exposure durations (C^n x t = k) using the default values of 3 and 1, respectively. Because of uncertainty in time-scaling from a 4-hour exposure duration to 10 minutes, the 10-minute value was set equal to the 30-minute value. A motion was made by Bob Benson and seconded by John Hinz to accept the values. The motion passed (Appendix O: 19 yes; 0 no; 1 abstain).

Summary of AEGL Values for Perchloryl Fluoride						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	1.8 ppm	1.8 ppm	1.5 ppm	0.92 ppm	0.60 ppm	NOEL in dog and rat (Greene et al., 1960)
AEGL–2 (Disabling)	5.0 ppm	5.0 ppm	4.0 ppm	2.5 ppm	1.2 ppm	One-third of the AEGL-3 values
AEGL–3 (Lethal)	15 ppm	15 ppm	12 ppm	7.5 ppm	3.7 ppm	4-hour hour non-lethal value in the dog (Greene et al. 1960)

Tellurium Hexafluoride (CAS No. 7783-80-4)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Roberta Grant, Texas

Cheryl Bast presented the data set and proposed AEGL derivation for tellurium hexafluoride (Attachment 12). Draft AEGL-1 values were not recommended due to insufficient data. In the

absence of empirical data, draft AEGL-2 values were set at one-third of the AEGL-3 values. The steep concentration response is evidenced by the fact that rabbits, guinea pigs, rats, and mice exposed to 5, 10, 25, 50, and 100 ppm tellurium hexafluoride for 4 hr all died. All mice exposed to 5 ppm for 1 hr died. All animals exposed to 1 ppm for 1 or 4 hr survived (Kimmerle, 1960). The highest concentration causing no mortality in a rabbit, guinea pig, rats, and mice (1 ppm for 4 hr) was used to derive draft AEGL-3 values (Kimmerle 1960). An intraspecies uncertainty factor of 3 was proposed because tellurium hexafluoride is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly among individuals. An interspecies uncertainty factor of 1 was proposed because the limited data suggest that the rabbit, guinea pig, rat, and mouse are similarly sensitive to the acute effects of tellurium hexafluoride. A modifying factor of 10 was applied to account for the potential effects of tellurium and the sparse database. Thus, the total adjustment is 30. To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points (10-, 30-, and 60-min) and n = 1 when extrapolating to longer time points (8 hr) using the $C^n \times t = k$ equation. The 30-minute AEGL-3 value was adopted for the 10-minute value due to the added uncertainty of extrapolating from a 4 hr time point to 10-minutes. After discussion, a motion was made by Bob Benson and seconded by John Hinz to accept AEGL values as presented with the exception that the 10-minute AEGL-3 value be derived by time scaling. Time scaling from 4-hr to 10-min is supported by a 1 hr study in multiple species exposed to 1 ppm (Kimmerle 1960). This exposure resulted in hyperpnea in all animals, a non life-threatening endpoint. Extrapolating that value and applying the total adjustment (uncertainty and modifying factor) of 30 yields a value of 2 ppm-min, suggesting that the proposed AEGL-3 10-min value (0.097 ppm x 10 min = 0.97 ppm-min) is protective. The motion passed (Appendix P: 19 yes; 2 no; 0 abstain).

Summary of AEGL Values for Tellurium Hexafluoride						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL−1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL−2 (Disabling)	0.032 ppm (0.32 mg/m^3)	0.022 ppm (0.22 mg/m^3)	0.018 ppm (0.18 mg/m^3)	0.011 ppm (0.11 mg/m^3)	0.0057 ppm (0.056 mg/m^3)	One-third of the AEGL-3 values (NRC 2001)
AEGL−3 (Lethal)	0.096 ppm (0.95 mg/m^3)	0.067 ppm (0.66 mg/m^3)	0.053 ppm (0.52 mg/m^3)	0.033 ppm (0.33 mg/m^3)	0.017 ppm (0.17 mg/m^3)	Highest concentration causing no mortality in a rabbit, guinea pig, rats, and mice (1 ppm, 4-hr) (Kimmerle, 1960)

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

SPECIAL PRESENTATIONS

Discussion of Data for Gasoline AEGLs

Presenter: Russell White, American Petroleum Institute

Russell White discussed the past, present, and future composition of gasoline and then discussed gasoline toxicology (Attachment 13). The American Petroleum Institute has sponsored studies on acute, subchronic, and chronic toxicity as well as studies on reproductive and developmental toxicity, neurotoxicity, genotoxicity, and neurotoxicity. Test materials included whole gasoline liquid, whole gasoline vapor, and various refinery streams. Dr. White provided the NAC with a CD containing study data that will be useful in deriving AEGL values for gasoline. Discussion of a draft AEGL TSD for gasoline will be scheduled for NAC-49.

Discussion of New Phosgene Data

Presenter: Jürgen Pauluhn, Bayer HealthCare

Jürgen Pauluhn discussed recent phosgene data (Attachment 14). Key discussion points included the fact that the apparent increased toxicity in recent studies is likely due to purer phosgene (no HCl contaminant), rodent vs. non-rodent animal models, time scaling (n=1 confirmed), delayed edema, and consistency of acute data with subchronic data. The new data suggest that the dog may be more appropriate than the rat as an animal model for phosgene risk assessment. There is an instant, although transient, change in breathing reflex in the rat; therefore, exposures of less than 30 minutes may result in false negative responses. The recent data also suggest that with regard physiology of the respiratory tract and acinar structure of the lung, dogs are more similar to humans than rodents. The NAC voted (unanimously by a show of hands; Appendix Q) to reconsider phosgene at the next meeting. The TSD should be re-written to incorporate the new data.

Discussion of Route to Route Extrapolation

Presenters: George Rusch (Honeywell) and Jürgen Pauluhn (Bayer HealthCare)

George Rusch and Jürgen Pauluhn both discussed route to route extrapolation as it pertains to risk assessment.

Dr. Rusch discussed factors influencing dose for food/drinking water vs. gavage vs. inhalation routes, and presented an example calculation (Attachment 15). He then discussed limitations of oral to inhalation extrapolation (often do not know α or ρ; toxicity of chemical can alter minute volume during exposure); uptake in upper respiratory system will lead to different distribution than uptake in lung; for poorly soluble particles, poor clearance from lung can lead to higher dose and for poorly soluble particles poor uptake from digestive system can lead to lower dose; oral uptake initially

enters entrohepatic circulation; whereas, inhalation uptake is into systemic circulation, and oral dosing often underestimates the toxicity by inhalation).

Dr. Pauluhn discussed absorption profile, metabolism (toxification vs. detoxification), toxicophoresis (GI vs. lung), and physiological responses specific to the respiratory tract (Attachment 16). He concluded that GI-tract dosing due to particles deposited in the extra-thoracic region have to be considered, non-inhalation routes do not necessarily predict what happens following inhalation, and that in the absence of PK-data and knowledge about the critical toxic mechanisms one should not extrapolate from oral to inhalation exposure (alternatively an adjustment factor of at least 25 must be applied).

ADMINISTRATIVE MATTERS

Future Meetings:
September 9-11, 2009: Research Triangle Park, NC

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

LIST OF ATTACHMENTS

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

Attachment 1. Meeting 48 agenda
Attachment 2. Meeting 48 attendee list
Attachment 3. Arsenic compound presentation
Attachment 4. Ricin presentation
Attachment 5. Cyanide salts presentation
Attachment 6. Phosgene oxime presentation
Attachment 7. PFIB presentation
Attachment 8. Oxamyl presentation
Attachment 9. Methomyl presentation
Attachment 10. Aldicarb presentation
Attachment 11. Perchloryl fluoride presentation
Attachment 12. Tellurium hexafluoride presentation
Attachment 13. Gasoling presentation
Attachment 14. Phosgene presentation
Attachment 15. Route to route presentation- Rusch
Attachment 16. Route to route presentation- Pauluhn
Attachment 17. NAC- 48 meeting certification

LIST OF APPENDICES

Appendix A. Ballot for approval of NAC-47 meeting highlights
Appendix B. Final NAC-47 Meeting Highlights
Appendix C. Ballot for no data/holding chemicals
Appendix D. Ballot for arsenic pentoxide and arsenic trichloride
Appendix E. Ballot for ricin
Appendix F. Ballot for sodium cyanide
Appendix G. Ballot for potassium cyanide
Appendix H. Ballot for calcium cyanide
Appendix I. Ballot for phosgene oxime
Appendix J. Ballot for PFIB
Appendix K. Ballot for oxamyl- first ballot
Appendix L. Ballot for oxamyl- second ballot
Appendix M. Ballot for methomyl
Appendix N. Ballot for aldicarb
Appendix O. Ballot for perchloryl fluoride
Appendix P. Ballot for tellurium hexafluoride
Appendix Q. Ballot for phosgene