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

April 13–15, 2010

Meeting-50 Highlights

Intercontinental Mark Hopkins Hotel
Number One Nobb Hill
San Francisco, CA

INTRODUCTION

Chairman George Rusch opened the meeting by calling for an introduction of all Committee members and guests. The Committee also welcomed the new technical support staff from SRC, Inc. SRC staff introduced themselves and provided a brief history of their professional experience. George commented that after 14 years and 50 meetings, this meeting would be his last as Chair of the Committee. Over the time that he has spent as the chair, the AEGL Committee had reviewed 316 documents and has developed 270 chemical Technical Support Documents (TSDs). The other 35 chemicals would have been completed, but due to lack of data, the Committee was not able to address those at this time. The National Academy has reviewed and finished 50 of the documents in the last 14 years. George mentioned the importance of the AEGL work and is encouraged by the progress that has been made. The Committee has provided values that are to be used on a global basis, and will continue to provide guidance in the future.

The draft meeting minutes from the NAC-49 meeting were reviewed. Comments were discussed for dimethyl phosphate, phosgene, and gasoline. For the summary for dimethyl phosphate (p.4, paragraph starting with "Two sets of AEGL-3 values were proposed…."), George Rusch noted that the second line should read "as used in the derivation of AEGL-2 values." Also for dimethyl phosphate (p. 4, final paragraph summarizing Susan Ripple's motion), George Rusch suggested that the "second approach" needs additional clarification. The clarification will be changed to read: "A motion was made by Susan Ripple, seconded by Jim Holler, to accept the AEGL-1 of NR, AEGL-2 values based on the Hazelton data, and AEGL-3 values based on the Biodynamics data." For the phosgene summary (pp.7–8, discussion supporting use of dog data as the basis for phosgene AEGL values), George Rusch noted that although AEGL-2 values were based on data from dogs, AEGL-3 values are based on rat data. George suggested that a statement be included to address why the rat data is acceptable as the basis of the AEGL-3 for phosgene. The following statement will be added before discussion of uncertainty: "The duration of exposure in this study is expected to minimize inaccuracy in the estimated lethality threshold due to bradypnea in the rats." Regarding the discussion of gasoline, George Woodall asked why a $BMCL_{10}$ was not used as point of departure (POD) when incidence data are available for the AEGL-1 values. George Rusch said that we can reconsider the POD and whether the asphyxiant data could be used to derive AEGL-3 values following public comment. No change is needed to the minutes. In addition to these discussions, George Woodall provided comments, including typographical errors, via email to Paul Tobin; Paul forwarded these to SRC to address. A motion to accept the minutes, with changes identified above was made by John Hinz (second by Allan Woolf) and passed unanimously (Appendix A). The Final NAC/AEGL-49 meeting highlights are included as Appendix B

The highlights of the NAC/AEGL-50 meeting are summarized below along with the Meeting Agenda (Attachment 1) and the Attendee List (Attachment 2).

CHEMICAL LIST

CHEMICAL REVISITS/STATUS UPDATES

Vinyl Chloride (CAS No. 75-01-4)

Staff Scientist: NA
Chemical Manager: Robert Benson, US EPA

Robert Benson presented the status and history of vinyl chloride (Attachment 3). AEGL-1 values were based on the study of Baretta et al. (1969) with 4–7 volunteers, two individuals experienced mild headache during 3.5 and 7.5 hours (3.5 hours, 0.5 hours break, 3.5 hours) of exposure to 491 ppm. A total uncertainty factor (UF) of 3 was used. Since the AEGL-1 values were based on human data, no interspecies extrapolation was used. The intraspecies UF of 3 was used. Duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods. The extrapolation to 10 minutes from a 3.5-hour exposure was considered justified because exposure of humans at 4000 ppm for 5 minutes did not result in headache (Lester et al., 1963). AEGL-2 values were based on prenarcotic effects observed in human volunteers. After a 5 minute exposure to 16,000 ppm vinyl chloride, 5 of 6 persons showed dizziness, lightheadedness, nausea, and visual and auditory dulling. At a concentration of 12,000 ppm, 1 of 6 persons showed dizziness and "swimming head, reeling". No effects were observed at 4000 ppm in this study. A concentration of 12,000 ppm was regarded as the no-effect level for impaired ability to escape. A total intraspecies UF of 3 was used to account for toxicodynamic differences among individuals. As unmetabolized vinyl chloride is responsible for the effect, no relevant differences in toxicokinetics were assumed. In analogy to other anesthetics the effects were assumed to be solely concentration dependent. Thus, after reaching steady state after approximately 2 hours of exposure, no increase in effect is expected. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n \times t = k$, using an n=2, based on data from Mastromatteo et al. (1960). Time extrapolation was performed from 5, 10, 30, and 60 minutes and 2 hours, where the steady state concentration was calculated. AEGL-3 values were based on cardiac sensitization and the no-effect level for lethality. Short term exposure (5 minutes) of dogs to vinyl chloride induced cardiac sensitization towards epinephrine (EC_{50}: 50,000 or 71,000 ppm in two independent experiments) (Clark and Tinston, 1973; Clark and Tinston, 1982). A total UF of 3 was used to account for toxicodynamic differences among individuals. As the challenge with epinephrine and the doses of epinephrine used represent a conservative scenario, no interspecies UF was used. Time scaling was as described from AEGL-2.

The Committee discussed time scaling ($C^n \times t = k$) for AEGL values. The COT Committee recommended using the same n-value for all AEGL-level values, because the mechanism of action for each AEGL-level effect is unknown. However, the NAC Committee did not feel comfortable using n=2 for AEGL-1 values (based on the anesthetic effect for headaches in people). The Committee decided (by a show of hands) to use the default values of n=3 for extrapolating to the shorter time, and n=1 extrapolating to the longer time intervals. For AEGL-3 derivation based on cardiac sensitization, not a central nervous system effect, and no mechanistic data are available. Therefore, the Committee agreed that a conservative approach to time scaling should be applied, and recommended using the time extrapolation default values. The recommendation of the Committee was to not change the slope factor n's or AEGL calculations for

AEGL-1 and AEGL-3 values. George Rusch noted that the write-up prepared by Bob Benson provided robust response to COT comments.

AEGL Values for Vinyl Chloride						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Non-disabling)	450 ppm 1200 mg/m^3	310 ppm 800 mg/m^3	250 ppm 650 mg/m^3	140 ppm 360 mg/m^3	70 ppm 180 mg/m^3	Mild headaches in 2/7 humans (Baretta et al., 1969); no effect level for notable discomfort.
AEGL-2 (Disabling)	2800 ppm 7300 mg/m^3	1600 ppm 4100 mg/m^3	1200 ppm 3100 mg/m^3	820 ppm 2100 mg/m^3	820 ppm 2100 mg/m^3	Mild dizziness in 1/6 humans (Lester et al., 1963); no effect level for impaired ability to escape.
AEGL-3 (Lethal)	12000 ppm* 31000 mg/m^3	6800 ppm* 18000 mg/m^3	4800 ppm* 12000 mg/m^3	3400 ppm 8800 mg/m^3	3400 ppm 8800 mg/m^3	Cardiac sensitization (Clark and Tinston, 1973, 1982); no effect level for lethality.

Diclorvos (CAS No. 62-73-7)

Staff Scientist: Julie Klotzbach, SRC, Inc.
Chemical Manager: Ernest Falke, US EPA

Julie Klotzbach presented a status update for the limited data set for dichlorvos (Attachment 4). In the current draft of the TSD, AEGL-1 values were based on human data (Hunter, 1970a) and AEGL-2 and AEGL-3 values were based on animal data (Atis et al., 2002; Dean and Thorpe, 1972a). The AEGL-1 values (0.11 ppm) were held constant across all time points because the data from Menz et al. (1974) showed no changes in effects over the 8-month time period during which the workers were exposed. The inhibition of plasma and erythrocyte cholinesterase activity did not increase with prolonged exposure. The AEGL-2 values were based on clinical signs observed in rats exposed for 45 minutes (Atis et al., 2002). At 10 and 15 mg dichlorvos/m^3 (aerosol), rats experienced dyspnea, increased salivation, excessive urination and defecation, and alveolar duct dilation and degeneration. The POD was 5 mg/m^3 for rats. No symptoms were observed, but histopathological findings included shorter epithelial cells in the trachea, loss of cilia from the ciliated cells of the trachea, alveolar interstitial thickening, capillary congestion, and extravasated erythrocytes. This POD (5 mg dichlorvos/m^3, vapor) is supported by a 2-year study in rats and is protective for the population. The AEGL-2 values were kept constant across all time points because the 2-year study showed that prolonged exposure would not result in an enhanced effect (Blair et al., 1976). The AEGL-3 values were based on the highest dichlorvos vapor exposure concentration for the longest duration without a lethal effect on mice (Dean and Thorpe, 1972a). Mice exposed to 72 mg/m^3 for 16 hours showed signs of organophosphate toxicity, but survived the exposure. The AEGL-3 values were kept constant across all time points because it is not expected that prolonged exposure would result in an enhanced effect based on the mouse data as well as longer term studies.

For all AEGL values, a total UF of 1 was applied. An interspecies UF of 1 was applied because human data were used to derive AEGL-1 values. An intraspecies UF of 1 was applied because an uncertainty

factor is not needed to account for age, sex, health status, or genetic polymorphisms with regard to dichlorvos exposure. The use of a higher uncertainty factor would result in AEGL-1 values below human exposure levels which did not result in any toxic response in a broad spectrum of the human population. Data also showed that the "A"-esterase that metabolizes dichlorvos are normally distributed in the population (Traverso et al., 1989).

The Committee discussed how dichlorvos could be compared to the other organophosphates, and if there is consistency among the organophosphates regarding the interspecies UF (e.g., 3 or 1). The Committee considered whether or not to recommend proceeding with the registration notice on the organophosphates. Ernie Falke noted that Bob Young (ORNL) is preparing a document to address concerns with the organophosphates. Once this document is received, it will provide information for the Committee to evaluate use of A-esterases to validate the proposed AEGL values. This also will allow for consistent approach for all the organophosphates. By show of hands, the Committee decided to table the dichlorvos document, and not to send the organophosphates to the NAS for review. Bob Young will have until September 1, 2010, to allow the Committee time to review dichlorvos before continuation of the discussion at the December 2010 meeting.

AEGL Values for Dichlorvos

Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.11 ppm (1 mg/m^3)	0.11 ppm (1 mg/m^3)	0.11 ppm (1 mg/m^3)	0.11 ppm (1 mg/m^3)	0.11 ppm (1 mg/m^3)	No effects in human volunteers exposed for 3–7.7 hours to 1 mg/m^3 (Hunter, 1970a).
AEGL-2 (Disabling)	0.56 ppm (5 mg/m^3)	0.56 ppm (5 mg/m^3)	0.56 ppm (5 mg/m^3)	0.56 ppm (5 mg/m^3)	0.56 ppm (5 mg/m^3)	Highest experimental exposure in rats without an AEGL-2 tier effect, 5 mg/m^3 (Atis et al., 2002).
AEGL-3 (Lethal)	8.0 ppm (72 mg/m^3)	8.0 ppm (72 mg/m^3)	8.0 ppm (72 mg/m^3)	8.0 ppm (72 mg/m^3)	8.0 ppm (72 mg/m^3)	Highest experimental exposure in mice without a lethal effect, 72 mg/m^3 (Dean and Thorpe, 1972a).

Ricin (CAS No. 9009-86-3)

Staff Scientist: Gary Diamond, SRC, Inc.
Chemical Manager: Jim Holler, ATSDR

Gary Diamond provided the status update of ricin (Attachment 5), and summarized the previous attempt to derive the AEGL-3 value based on the Gomez et al. (2009). AEGL-3 derivation results were compared to the Griffiths et al. (1995) and the Smallshaw et al. (2006) study.

The use of measured (Gomez et al., 2009) versus estimated (Griffiths et al., 1995) exposure concentrations and the presence of different minute inhalation volumes for the animals was discussed. By back calculating the minute inhalation volumes, the values of the Gomez et al. (2009) study were 1/10th of the Griffiths et al. (1995). Before further review, it was decided that SRC would contact Gomez and

point out the minute volume issues, and ask for an explanation to verify the numbers in question. A list of talking points will be generated, and a letter would be drafted by Gary Diamond, given to Paul Tobin to send to the study authors.

After discussion of the methodology and comparison of the two studies, the Committee decided not to change the basis of the AEGL-3 values. It was noted that the current AEGL-3 values based on data from the Gomez et al. (2009) study may be too high. However, the Committee decided that no changes to AEGL values would be made until issues are shared with study authors and additional information/clarification regarding inhalation minute volume is received from study authors.

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

Hydrogen Bromide (CAS No. 10035-10-6)
Hydrogen Iodide (CAS No. 10034-85-2)

Staff Scientist: Heather Carlson-Lynch, SRC, Inc.
Chemical Manager: Ernie Falke, US EPA, and Susan Ripple, Dow Chemical Company

Heather Carlson-Lynch summarized the changes that were made in response to the NAS comments (Attachment 6). The history of the interim technical support document for these chemicals was reviewed. In the absence of acute data for hydrogen iodide, the AEGL-1, AEGL-2, and AEGL-3 values for hydrogen iodide were derived on the data set for hydrogen bromide.

Data on the relative toxicities of hydrogen fluoride (HF), hydrogen chloride (HCl), and hydrogen bromide (HBr) for the endpoint of lethality and some data comparing HBr to other hydrogen halides are available. Three rodent studies utilizing different exposure durations show that HF is more lethal than HCl (Higgins et al., 1972; MacEwen and Vernot, 1972; Rosenholtz et al., 1963; Wohlslagel et al., 1976). For both the rat and mouse, HF is also more lethal than HBr (MacEwen and Vernot, 1972). Data from the same laboratory (MacEwen and Vernot, 1972; Wohlslagel et al., 1976) show that HCl and HBr have similar 1-hour LC_{50} values of 3124 ppm and 2858 ppm, respectively. Data on the nonlethal toxicity of the three hydrogen halides (Stavert et al., 1991) suggest that HF and HCl cause more severe nasal lesions than HBr, and, unlike HBr, cause damage extending deeper into the nasal cavity under the same exposure conditions. Hydrogen bromide and HF exposure resulted in similar decreases in ventilation rate (~25%), while the decrease associated with HCl exposure was smaller (Stavert et al., 1991).

The major COT comment addressed was the rationale for selection of 1300 ppm for the POD for the AEGL-2 values instead of 1000 ppm. At 1300 ppm, mortality was observed in the animals. A new POD

for AEGL-2 values (1000 ppm) was proposed. Exposure of male rats to 1000 ppm for 30 minutes resulted in lesions of the nasal passages. Because the severity of the lesions may exceed the definition of AEGL-2 and because this concentration is close to the calculated $BMCL_{05}$ of 1239 ppm used as the POD for the AEGL-3, the 1000 ppm concentration was divided by a modifying factor of 2. Furthermore, the intraspecies UF of 3 is consistent with that used for other hydrogen halides. The intraspecies UF of 3 for HCl is supported by the steep concentration-response curve, which indicates little interindividual variability and by the fact that larger uncertainty factors would not be supported by the total data set, including the data on exercising asthmatics. It is assumed that the action of all hydrogen halides on the respiratory tract is the same (shown by the data of Stavert et al., 1991); therefore, protection of exercising asthmatics for one chemical would be protective of asthmatics at a similar concentration of another hydrogen halide. Thus, the total uncertainty and modifying factor adjustment was 20. A time scaling value ($C^n \times t = k$) of n=1 was used, as was done for HCl. Because all three chemicals (HBr, HF, and HCl) are well scrubbed in the upper respiratory tract at moderately high concentrations, the 4- and 8-hour AEGL-2 values were set equal, as was done for HF and HCl (NRC, 2004). The 4- and 8-hour values were derived by applying a modifying factor of 2 to the 1-hour AEGL-2 value because time scaling would yield 4- and 8-hour values of 6.3 and 3.1; these values are close to the AEGL-1 values tested in the Connecticut Department of Health (1955) study. The same modifying and uncertainty factors were applied to hydrogen iodide (HI), which is expected to be less toxic than HBr.

A motion was made by John Hinz and seconded by Rick Niemeier to revise the AEGL-2 values for HBr and HI using the new basis of POD of 1000 ppm, applying a combined UF of 10 and a modifying factor of 2. The revised AEGL-2 values for both HBr and HI are 10-minutes: 150 ppm; 30-minutes: 50 ppm; 1-hour: 25 ppm; 4- and 8-hour: 13 ppm (HBr: Appendix C: Yes: 19; No: 0; Abstain: 4; HI: Appendix D: Yes: 19; No: 0; Abstain: 4).

AEGL Values for Hydrogen Bromide and Hydrogen Iodide

Compound	Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
Hydrogen Bromide	AEGL-1 (Nondisabling)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	1.0 ppm (3.3 mg/m^3)	Nasal irritation (Connecticut State Department of Health, 1955).
	AEGL-2 (Disabling)	150 ppm (500 mg/m^3)	50 ppm (170 mg/m^3)	25 ppm (83 mg/m^3)	13 ppm (43 mg/m^3)	13 ppm (43 mg/m^3)	Lesions – rat (Kusewitt et al., 1989; Stavert et al., 1991).
	AEGL-3 (Lethal)	740 ppm (2442 mg/m^3)	250 ppm (825 mg/m^3)	120 ppm (396 mg/m^3)	31 ppm (102 mg/m^3)	31 ppm (102 mg/m^3)	Benchmark dose ($BMCL_{05}$) – rat (MacEwen and Vernot, 1972).
Hydrogen Iodide	AEGL-1 (Nondisabling)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	1.0 ppm (5.2 mg/m^3)	Analogy with hydrogen bromide.
	AEGL-2 (Disabling)	150 ppm (780 mg/m^3)	50 ppm (260 mg/m^3)	25 ppm (130 mg/m^3)	13 ppm (68 mg/m^3)	13 ppm (68 mg/m^3)	Analogy with hydrogen bromide.
	AEGL-3 (Lethal)	740 ppm (3870 mg/m^3)	250 ppm (1307 mg/m^3)	120 ppm (628 mg/m^3)	31 ppm (162 mg/m^3)	31 ppm (162 mg/m^3)	Analogy with hydrogen bromide.

Chlorine Pentafluoride (CAS No. 13637-63-3)

Staff Scientist: Heather Carlson-Lynch, SRC, Inc.
Chemical Manager: William Bress, ASTHO

Heather Carlson-Lynch provided a review of available data and a draft of AEGL values for chlorine pentafluoride (Attachment 7). The two issues for considerations were: (1) to not recommend AEGL-1 values due to inadequate data; and (2) to revise the AEGL-2 and AEGL-3 values to correct rounding errors for *n* (*n* was rounded from 1.89 to 2; recommend rounding to 1.9). In response to COT comments, it was proposed to recalculate 4- and 8-hour AEGL-2, and all AEGL-3 values using n=1.9 ($C^{1.9} \times t = k$).

Without data supporting exposure durations longer than 10 minutes, AEGL-1 values were not recommended due to a conflict with the standard operating procedure for over extrapolating 4- and 8-hour from the 10-minute time interval. The AEGL-2 values were based on the series of acute studies with monkeys, dogs, rats, and mice (MacEwen and Vernot, 1972, 1973). AEGL-2 level effects (sensory irritation and reversible mild lung congestion) were observed in monkeys, rats, and mice following exposure to 30 ppm for 10 minutes, 20 ppm for 30 minutes, or 10 ppm for 60 minutes or following exposure of dogs to 30 ppm for 10 minutes. At all exposures, effects were similar in the four species. For the 10-, 30-, and 60-minute exposure durations, respective values of 30, 20, and 10 ppm were used as the POD for AEGL-2 values. A total UF of 10 (3 for intraspecies and 3 for interspecies) was applied. Time scaling ($C^n \times t = k$), was based on the rat data set, with n=1.9. The AEGL-3 values were based on a lethality study with rats (Darmer et al., 1972). Of four species tested at exposure durations of 15, 30, and 60 minutes, the lethality data for rats showed the best concentration-exposure duration relationship. The 60-minute concentration resulting in no deaths in rats (80 ppm) was used as the POD. Total uncertainty factors and time-scaling was applied as described for AEGL-2 values.

After thorough discussion, a motion was made by Robert Benson and seconded by Henry Anderson to correct rounding errors for the calculations of the AEGL-2 and AEGL-3 values, using the corrected value of *n* (changed from n=2 to n=1.9). Resulting changes in AEGL values are less that 10%. Values for AEGL-2 are: 10-minutes: 3 ppm; 30-minutes: 2 ppm; 1-hour: 1 ppm, 4-hour: 0.48 ppm; and 8-hour: 0.33 ppm. The values for AEGL-3 are: 10-minutes: 21 ppm; 30-minutes: 12 ppm; 1-hour: 8 ppm, 4-hour: 3.9 ppm; and 8-hour: 2.7 ppm. It was also stated that the abbreviation "NR" was also defined as "inadequate data". The motion passed. (Appendix E: Yes: 18; No: 0; Abstain: 6).

AEGL Values for Chlorine Pentafluoride						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1[a] (Nondisabling)	NR	NR	NR	NR	NR	Inadequate data.
AEGL-2 (Disabling)	3.0 ppm (16 mg/m^3)	2.0 ppm (11 mg/m^3)	1.0 ppm (5.3 mg/m^3)	0.48 ppm (2.6 mg/m^3)	0.33 ppm (1.8 mg/m^3)	Sensory irritation, mild lung congestion – monkey, dog, rat, and mouse (MacEwen and Vernot, 1972; 1973).
AEGL-3 (Lethal)	21 ppm (112 mg/m^3)	12 ppm (64 mg/m^3)	8.0 ppm (43 mg/m^3)	3.9 ppm (21 mg/m^3)	2.7 ppm (14 mg/m^3)	Highest 1-hr non-lethal concentration in rats (Darmer et al., 1972).

[a] There is no information on the odor threshold. The odor is described as pungent and suffocating.
NR = Not recommended.

Bromine Pentafluoride (CAS No. 7789-30-2)

Staff Scientist: Heather Carlson-Lynch, SRC, Inc.
Chemical Manager: William Bress, ASTHO

Heather Carlson-Lynch summarized the data set for bromine pentafluoride (Attachment 8). AEGL-1 values were not derived due to inadequate data. Sensory irritation and reversible mild lung congestion were observed in monkeys, rats, and mice following exposures to 30 ppm for 10 minutes, 20 ppm for 30 minutes, or 10 ppm for 60 minutes and following exposure of dogs to 30 ppm for 10 minutes. For all exposures, effects were similar in the four species, although the 10-minute, 30 ppm exposure was slightly more irritating. Therefore, separate data points, i.e., the 10-, 30-, and 60-minute values, were used for the relevant AEGL-2 exposure durations. For contact irritants without additional systemic effects, interspecies and intraspecies UFs of 3 each for a total of 10 are generally applied (NRC, 2001). The interspecies UF of 3 is supported by the similar toxic effects seen in four species of animals exposed to the same concentrations of chlorine pentafluoride (ClF_5) in the key study. In addition, 60-minute LC_{50} values differed by a factor of 3 among the four species. The total UF of 10 was applied to the ClF_5 values. In setting the bromine pentafluoride (BrF_5) values, a modifying factor was not applied to the ClF_5 data because uncertainties stemming from the limited database were addressed by setting the BrF_5 values equal to those for ClF_5 despite its lower toxicity compared with ClF_5. Previously, the 4- and 8-hour values were extrapolated from the 1-hour value using a value of 2, derived from lethality data of the rat ($C^n \times t = k$). Time scaling ($C^n \times t = k$) of ClF_5, however, was discussed, and it was decided that based on the rat data set, the n=2 would be adjusted to n=1.9. AEGL-3 values for BrF_5 are based on the highest non-lethal value in the rat study of Dost et al. (1970), 500 ppm for 40 minutes. A total UF of 10 (3 for intraspecies and 3 for interspecies) was applied. Time-scaling used default values for n of 3 for shorter time intervals and 1 for longer time intervals (NRC, 2001). No change was proposed for AEGL-3 values.

A motion was put forth by John Hinz, and seconded by Alan Becker, to change the AEGL-2 values for bromine pentaflouride at the 4- and 8-hour values to reflect the rounding of the value of n ($C^n \times t = k$). The changes were proposed to change the n=2 to n=1.9, to provide a more accurate calculation. The new 4- and 8-hour AEGL-2 values are 0.48 and 0.33 ppm, respectively. The motion has carried. (Appendix F: Yes: 19; No: 0; Abstain: 5)

AEGL Values for Bromine Pentafluoride						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1[a] (Nondisabling)	NR	NR	NR	NR	NR	No data.
AEGL-2[b] (Disabling)	3.0 ppm (21 mg/m^3)	2.0 ppm (14 mg/m^3)	1.0 ppm (7.2 mg/m^3)	0.48 ppm (3.4 mg/m^3)	0.33 ppm (2.4 mg/m^3)	Based on analogy with chlorine pentafluoride.
AEGL-3 (Lethal)	79 ppm (565 mg/m^3)	55 ppm (393 mg/m^3)	33 ppm (236 mg/m^3)	8.3 ppm (59 mg/m^3)	4.2 ppm (30 mg/m^3)	Highest non-lethal concentration in the rat (Dost et al., 1970).

[a] The odor threshold is unknown; the odor has been described as sharp and penetrating.
[b] The 10- and 30-minute and 1-hour AEGL-2 values are based on separate data points.
NR: Not recommended; AEGL-1 values are not recommended due to a lack of data.

Chloroacetone (CAS No. 78-95-5)

Staff Scientist: Julie Klotzbach, SRC, Inc.
Chemical Manager:

Julie Klotzbach presented a summary of the limited data for chloroacetone (Attachment 9). Chloroacetone breaks down quickly to HCl, which produces irritant effects. Little data was available to evaluate the effects in humans, but eye and dermal irritation was reported. Information regarding the mechanism of toxicity of chloroacetone was not located. Draft AEGL-1 values were not recommended due to insufficient data. In the absence of empirical data, the AEGL-2 values for 30-minutes, 1-, 4-, and 8-hours were based upon a 3-fold reduction in the AEGL-3 values. The 30-minute AEGL-2 value was adopted as the 10-minute AEGL-2 value because of the human case report suggesting that exposure to 4.7 ppm causes immediate, severe irritation (Sargent et al., 1986). The estimated 1-hour lethality threshold (in male rats) of 131 ppm ($BMCL_{05}$) was used as the basis of the AEGL-3 values (Arts and Zwart, 1987). Interspecies and intraspecies UFs of 3 each were be applied because chloroacetone is highly irritating and clinical signs are 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. The interspecies UF of 3 is also supported by the fact that data suggest little species variability with regard to lethality from oral and dermal exposure to chloroacetone (rat oral LD_{50} values: 100–141 mg/kg; mouse oral LD_{50} values: 127–141 mg/kg; rabbit dermal LD_{50} = 141 mg/kg), and the 1-hour LC_{50} of 500 ppm for male and female rats (Arts and Zwart, 1987) gives an approximate dose of 114 mg/kg, which corresponds to the oral LD_{50} values (assuming 100% retention, 245 mL minute volume and a rat body weight of 250 g). The intraspecies UF of 3 is also considered sufficient because data from the more sensitive males were used as the POD. For time scaling, data were unavailable for an empirical derivation of *n* for chloroacetone. Therefore, an *n* of 3 was applied to extrapolate to the 10- and 30-minute time periods, and an *n* of 1 was applied to extrapolate to the 4- and 8-hour time periods to provide AEGL values that would be protective of human health (NRC, 2001).

After the discussion, the Committee decided to use the 1-hour number for AEGL-2 at 10 and 30 minutes because exposure of a single human to 4.7 ppm (combination of inhalation and dermal exposure from a burst pipe) resulted in significant irritation (Sargent et al., 1986), although there appeared to be a lack of information of how the exposure concentration was measured and the dermal exposure.

An initial motion was made by Bob Benson, seconded by John Hinz, to revise the chloroacetone AEGL-2 values at 10 and 30 minutes to 4.4 ppm and to revise the 8-hour AEGL-3 value from 3.3 ppm to 1.6 ppm as the result of continuation of time extrapolation. The 8-hour AEGL-2 values would also change from 1.1 ppm to 0.53 ppm, because AEGL-2 values were based on a one-third reduction of AEGL-3 values. However, after further discussion, Bob Benson withdrew his motion to change the AEGL-2 values, and moved to keep the original values (a shown in table below). This was agreed by the Committee by show of hands. The motion to change the 8-hour AEGL-2 and AEGL-3 values carried. (Appendix G: Yes: 19; No: 0; Abstain: 5)

AEGL Values for Chloroacetone						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1[a] (Nondisabling)	NR*	NR	NR	NR	NR	Insufficient Data
AEGL-2 (Disabling)	5.5ppm (21 mg/m^3)	5.5 ppm (21 mg/m^3)	4.4 ppm (17 mg/m^3)	1.1 ppm (4.2 mg/m^3)	0.53 ppm (2.0 mg/m^3)	One-third of AEGL-3 values.
AEGL-3 (Lethal)	24 ppm (91 mg/m^3)	17 ppm (65 mg/m^3)	13 ppm (49 mg/m^3)	3.3 ppm (13 mg/m^3)	1.6 ppm (6.1 mg/m^3)	Estimated lethality threshold for male rats (BMD_{05}) (Arts and Zwart, 1987).

NR: Not Recommended; numeric values for AEGL-1 are not recommended because data are not available.
[a] Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

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

Staff Scientist: Gary Diamond, SRC, Inc.
Chemical Manager: George Rusch, Honeywell, Inc.

Gary Diamond presented the data set for selenium hexafluoride (Attachment 10). The document was previously prepared by Cheryl Bast, reviewed by the NAS and has been redistributed to the Committee for review. In response to comments, the request for the discussion of the toxicity mechanism of the hydrolysis products is the selenium oxide was expanded.

AEGL-1 values were based on the no-effect level irritation in the guinea pig, rabbit, rats, and mice (1 ppm for 4-hours) (Kimmerle, 1960). Interspecies and intraspecies UFs of 3 each were applied because selenium hexafluoride is highly irritating and corrosive (effects at AEGL-1 and AEGL-3 concentrations is most likely to be minor irritation to severe irritation/corrosion, respectively), and toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. 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. The intraspecies UF of 3 is further supported by the 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) which implies limited intraindividual variability (Kimmerle, 1960). A modifying factor of 3 was applied to account for potential effects of the selenium moiety and the sparse database. Thus, the total adjustment for total UF and modifying factor of 30 was applied. To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, time scaling was performed using $C^n \times t = k$. Default values of n=3 was used to extrapolate to shorter time points and n=1 to extrapolate to longer time points. The 30-minute AEGL-1 value was also adopted as the 10-minute AEGL-1 value due to the added uncertainty of extrapolating from 4 hours to 10 minutes. Although AEGL-1 values might normally be held constant across all time points because minor irritation does not vary over time, time scaling was used for selenium hexafluoride AEGL-1 values to account for any potential effects resulting from the selenium moiety.

In the absence of empirical data for AEGL-2 derivation, AEGL-3 values were divided by 3 to obtain AEGL-2 values for selenium hexafluoride. This approach is 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).

To derive AEGL-3 values, the highest concentration causing no mortality in the guinea pig, rabbit, rats, and mice (5 ppm for 4-hours) was used (Kimmerle, 1960). A total UF of 10 was applied and a modifying factor of 3 was applied, as described for derivation of AEGL-1 values. Time-scaling was applied as described for derivation of AEGL-1 values. The 30-minute AEGL-3 value was also adopted as the 10-minute AEGL-3 value due to the added uncertainty of extrapolating from a 4-hour time point to 10-minutes.

After further discussion, it was concluded that since there are no recommended changes to AEGL values, and the Committee considered the current responses to the NAS comments adequate. It was decided that the document and responses to the NAS comments would be forwarded to the NRC.

AEGL Values for Selenium Hexafluoride						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	0.067 ppm (0.53 mg/m^3)	0.067 ppm (0.53 mg/m^3)	0.053 ppm (0.42 mg/m^3)	0.033 ppm (0.26 mg/m^3)	0.017 ppm (0.13 mg/m^3)	NOEL for irritation in rabbit, guinea pig, rats, and mice (1 ppm, 4-hr) (Kimmerle, 1960).
AEGL–2 (Disabling)	0.11 ppm (0.87 mg/m^3)	0.11 ppm (0.87 mg/m^3)	0.087 ppm (0.69 mg/m^3)	0.057 pm (0.45 mg/m^3)	0.028 ppm (0.22 mg/m^3)	One-third of the AEGL-3 values.
AEGL–3 (Lethal)	0.33 ppm (2.6 mg/m^3)	0.33 ppm (2.6 mg/m^3)	0.26 ppm (2.1 mg/m^3)	0.17 ppm (1.3 mg/m^3)	0.083 ppm (0.66 mg/m^3)	Highest concentration causing no mortality in rabbit, guinea pig, rats, and mice (1 ppm, 4-hr) (Kimmerle, 1960).

Methyl Isothiocyanate (CAS No. 556-61-6)

Staff Scientist: NA
Chemical Manager: Ernest Falke

Ernest Falke gave status update for methyl isothiocyanate (Attachment 11), and discussed public comments. A public comment was made that slight eye irritation at 0.8 ppm could be used as the basis for derivation of AEGL-1 values. The Committee agreed with the proposed response that this approach is not appropriate, as slight eye irritation is considered below the threshold for notable irritation that would typically be used as the threshold for the AEGL-1. No other effects were identified that are consistent with AEGL-1 level effects. Draft AEGL-2 values were based upon a 3-fold reduction in the AEGL-3 values, which were the highest nonlethal concentration obtained for 1- and 4 hours. Other public comments made (see Attachment 11) also did not result in changes to AEGL values. Ernest Falke recommended that the Committee raise AEGL values for methyl isothiocyanate from proposed to interim status. Bob Benson made a motion, seconded by David Freshwater, to raise the methyl isothiocyanate AEGL values from proposed to interim status. The motion passed. (Appendix H: Yes: 19; No: 0; Abstain: 5).

Ernest noted that he would write his analysis, and provide an electronic copy to the DFO, Paul Tobin.

Summary of AEGL Values for Methyl Isothiocyanate						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	0.80 ppm (2.4 mg/m^3)	NOAEL for eye irritation at several time points – humans (Russell and Rush, 1996).
AEGL-2 (Disabling)	43 ppm (130 mg/m^3)	29 ppm (87 mg/m^3)	23 ppm (69 mg/m^3)	9.0 ppm (27 mg/m^3)	4.3 ppm (13 mg/m^3)	AEGL-3 values divided by 3; steep concentration-response curve for lethality (NRC, 2001).
AEGL-3 (Lethal)	130 ppm (390 mg/m^3)	88 ppm (260 mg/m^3)	70 ppm (210 mg/m^3)	27 ppm (81 mg/m^3)	13 ppm (39 mg/m^3)	1- and 4-hr highest non-lethal concentrations – rat (Clark and Jackson, 1977; Jackson et al., 1981)[3].

REVIEW of PRIORITY CHEMICALS

Carbon Dioxide (CAS No. 124-38-9)

Staff Scientist: Gary Diamond, SRC, Inc.
Chemical Manager: Marcel van Raaij, National Institute of Public Health & Environmental (RIVM)

Gary Diamond presented the evaluation and summary of carbon dioxide (CO_2) (Attachment 12). AEGL-1 levels for CO_2 were based upon subclinical, asymptomatic visual effects in human volunteer subjects following 1-hour exposure to 2.5% (25,000 ppm) CO_2 (Sun et al., 1996; Yang et al., 1997). The interspecies UF was 1 because AEGL-1 development was based upon human data. Because available studies do not identify or imply a sensitive population, an intraspecies UF of 1 was applied. Time-scaling was not applied. The AEGL-2 values were derived based upon data in humans indicating that 5–7% (50,000–70,000 ppm) CO_2 at various exposure durations produces dyspnea, headaches, burning eyes, dizziness, anxiety, and at concentrations ≥7% (70,000 ppm) unconsciousness. A total UF of 1 was applied, but no time-scaling was applied, as discussed for derivation of AEGL-1 values. Data for derivation of AEGL-3 values were considered inadequate.

The focus of the discussion was whether or not the Committee was in the position to develop AEGL-3 values, and if so, to come up with a series of recommendations for collecting any additional data. When considering the amount of human lethality data, deviations of AEGL values is very important. One recent lethality study that was not included in the TSD is the TNO (2010) study, which found mortality in rats exposed to concentrations greater than 40% CO_2 for 10-minutes to 6-hours. This could be a basis for the lethality POD.

The Committee recommended the next steps of analysis: revise and revisit the way the CO_2 interacts with the body. It was also noted that there needs to be a clear discussion in the document that addresses asphyxiation. Discussion of time-scaling needs to be strengthened beyond the pharmacokinetics of CO_2.

AEGL Values for Carbon Dioxide						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	25,000 ppm	25,000 ppm	25,000 ppm	25,000 ppm	25,000 ppm	Subclinical effects on vision; 1-hr exposure of human subjects to 2.5% (25,000 ppm) CO_2 (Sun et al., 1996; Yang et al., 1997). UF=1x1; no time scaling.
AEGL-2 (Disabling)	50,000 ppm	50,000 ppm	50,000 ppm	50,000 ppm	50,000 ppm	Dyspnea, nausea, chills (anxiety in a sensitive subgroup) exposed to 5% (50,000 ppm) CO_2; exposure durations up to 12 hrs; little or no effect in some individuals (Brown, 1930b; Woods et al., 1988). UF=1x1; no time scaling.
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Not recommended: insufficient data with which to estimate a lethality threshold or exposure concentration-duration relationship.

Red Phosphorus, Butyl Rubber (CAS No. 7723-14-0)

Staff Scientist: Julie Klotzbach, SRC, Inc.
Chemical Manager: Glenn Leach, U.S. Army Center for Health Promotion & Preventive Medicine

Julie Klotzbach presented a summary of the limited data for red phosphorus (RP), butyl rubber (BR) (Attachment 13). The composition (4% black powder) of RP/BR smoke has high phosphoric acid content, and the contribution of the butyl rubber to the toxicity of RP/BR smoke has not been investigated. Draft AEGL-1 values were not recommended due to inadequate data. AEGL-2 derivation, the critical effect/POD respiratory distress in dogs exposed to RP/BR smoke at a concentration of 1519 mg/m^3 for 30 minutes (Ct = 760 $mg \cdot hour/m^3$) (Weimer et al., 1977). The same response was also observed in rats (Weimer et al., 1977), but at a somewhat greater exposure (1128 mg/m^3 for 1 hour; Ct = 1128 $mg \cdot hour/m^3$). A total UF of 10 was applied (3 for interspecies variability and 3 for intraspecies variability). Data were not available to empirically derive a time-scaling exponent, *n*, in the equation $C^n \times t = k$; therefore, default values for *n* were used (*n*=3 for extrapolation to shorter time points and *n*=1 for extrapolation to longer time points). The AEGL-2 values are consistent with an occupational exposure report noting significant but reversible symptoms of respiratory distress and irritation of the eyes and mucous membranes following exposure to RP/BR smoke at concentrations of 100–700 mg/m^3 for less than 15 minutes. For AEGL-3 derivation, the 1-hour lethality threshold estimated as a 1-hour $BMCL_{05}$ of 2281 mg/m^3 in rats was used as the POD. A total UF of 10 (3 for interspecies variability and 3 for intraspecific variability) was applied. Although lethality data were available for only two species, exposure-response data for nonlethal effects in dogs, rats, and rabbits showed about a 3-fold variability when comparing cumulative exposure (Ct) products. Because pulmonary effects associated with lethality

are likely a continuum of the same mode of action with limited variability across species, the interspecies UF was limited to 3. Red phosphorus/butyl rubber smoke appears to act as a direct-contact irritant, likely the result of ortho-phosphoric acid formation. Under the assumption that such a direct-contact activity would also be involved in tissue damage resulting in potentially lethal pulmonary damage and that these processes would not vary appreciably among individuals, the intraspecies UF was limited to 3. Additional uncertainty factor application would result in AEGL-3 values inconsistent with the AEGL-2 values, which are supported by human exposure data. Time scaling ($C \times t = k$, where n=1 or 3) was performed as described for AEGL-2.

After discussing the key data limitations regarding POD for the AEGL-2 and AEGL-3 values, it was decided by the Committee that the data must be standardized across studies. George Rusch recommended that the Committee defer further discussion of the red phosphorus/butyl rubber technical support document until SRC can compare the red phosphorus and RP/BR TSDs. It was noted that is important to ensure that common dosemetric is used and that data are reported using a consistent dose metric in both TSDs. For consistency in the analysis, it was also agreed that the unit of dose as red phosphorus should be reported as elemental P (mg/m^3). The Committee recommended deferring publication in the Federal Register until these issues are resolved.

AEGL Values For Red Phosphorus/Butyl Rubber Smoke						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data.
AEGL-2 (Disabling)	220 mg/m^3	160 mg/m^3	76 mg/m^3	19 mg/m^3	9.5 mg/m^3	Transient respiratory tract distress in dogs (Weimer et al., 1977); 1519 mg/m^3 for 30 min; UF=3x3; n=1or 3.
AEGL-3 (Lethality)	410 mg/m^3	290 mg/m^3	230 mg/m^3	57 mg/m^3	29 mg/m^3	Rat 1-hr lethality threshold estimated by $BMCL_{05}$ of 2281 mg/m^3 (Aranyi, 1983); UF=3x3; n=1or 3.

NR: not recommended; absence of AEGL-1 values does not imply that exposure below AEGL-2 values are without effect.

Monoethanolamine (CAS No. 141-43-5)

Staff Scientist: Heather Carlson-Lynch, SRC, Inc.
Chemical Manager: Lynn Beasley, US EPA

Heather Carlson-Lynch presented a summary of the available data and an overview of the development of proposed AEGL values for monoethanolamine (Attachment 14). AEGL-1 values were based on the highest exposure concentration (12 ppm) that did not cause immediate signs of discomfort or irritation in dogs, rats, and guinea pigs in the continuous exposure study (Weeks et al., 1960). The 12 ppm no-effect level was adopted as the POD for derivation of the 8-hour AEGL-1 value. For the purpose of AEGL derivation, it was assumed that the cage-side observations of irritability and hypoactivity were related to irritation of the respiratory tract and skin. Thus, time scaling was not performed because irritation is dependent on concentration rather than time. A total UF of 10, including values of 3 for interspecies variability and 3 for intraspecies variability, was applied to derive the AEGL-1 values.

AEGL-2 is based on information from initial (day 1) observations in the continuous exposure study by Weeks et al. (1960). The 26 ppm exposure level was also selected because it is the only intermediate

concentration (for which there are toxicity data) between the POD used for the 8-hour AEGL-3 value (75 ppm) and the no-effect level used as the POD for the 8-hour AEGL-1 value (12 ppm). At the next higher concentration (102 ppm), the dogs exhibited the following effects: immediate behavioral changes, salivation, and vomiting within a few hours; hypoactivity within 24 hours; lethargy by 48 hours; and mortality after 25 days. Empirical data that can serve as the basis for estimating the value of *n* are not available. In the absence of empirical data, the default temporal scaling value of 3 (NRC, 2001) was used to extrapolate from the 8-hour POD of 26 ppm to shorter time points ($C^3 x\ t = k$). A total UF of 10 was applied to derive the AEGL-2 values. The 10- and 30-minute AEGL-3 values were estimated from the 15-minute POD of 192 ppm, while the 1-, 4-, and 8-hour values used as a POD the 8-hour lower-bound lethality threshold of 75 ppm. The 10- and 30-minute AEGL-3 values were extrapolated from the 15-minute POD using the $C^n x\ t = k$ (NRC, 2001). The 1- and 4-hour values were set equal to the 8-hour value due to similarities between the estimated lethality threshold (77 ppm) based on data from the 1-hour study of guinea pigs (Kettering Laboratory, 1957) and the lower-bound lethality threshold (75 ppm) in the continuous (23.75 hours/day) exposure study of guinea pigs. For all of the AEGL-3 derivations, a total UF of 10, including 3 for interspecies variability and 3 for intraspecies variability, was applied.

For AEGL-3 values, a 15-minute observed nonlethal concentration of 192 ppm (derived from data in male guinea pigs reported by Kettering Laboratory, 1957) was selected as the POD for derivation of the 10- and 30-minute AEGL-3 values. Extrapolations from the 15-minute value were made using the default temporal extrapolations ($C^n x\ t = k$, where n=3 for extrapolation to shorter duration and n=1 for extrapolation to longer duration; NRC, 2001). Empirical data with which to estimate the value of *n* were not available.

Benchmark dose modeling of the acute lethality data in guinea pigs, rats, and mice data was problematic. Modeling of the data from the 15-minute study resulted in widely divergent $BMCL_{05}$ and BMC_{01} values. As a consequence, these data were questionable and will require further review. Due to issues pertaining to the reliability of the exposure concentrations, durations and the physical properties of monoethanolamine (i.e., exposures going beyond saturation), the Committee decided to table the report, review the primary literature, and return in December 2010 to re-evaluate the data sets.

AEGL Values for Monoethanolamine						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoints (Reference)**
AEGL-1 (Nondisabling)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	1.2 ppm (3.0 mg/m^3)	No behavioral changes or skin irritation over 24 hrs (Weeks et al., 1960).
AEGL-2 (Disabling)	9.4 ppm (24 mg/m^3)	6.6 ppm (17 mg/m^3)	5.2 ppm (13 mg/m^3)	3.3 ppm (8.3 mg/m^3)	2.6 ppm (6.5 mg/m^3)	Immediate behavioral changes and skin irritation followed by lethargy (Weeks et al., 1960).
AEGL-3 (Lethal)	22 ppm (55 mg/m^3)	9.6 ppm (24 mg/m^3)	7.5 ppm (19 mg/m^3)	7.5 ppm (19 mg/m^3)	7.5 ppm (19 mg/m^3)	Observed nonlethal concentration in guinea pigs exposed for 15–60 min (Kettering Laboratory, 1957) and lower bound lethality threshold for guinea pigs in continuous exposure study (Weeks et al., 1960).

Hydrogen Selenide (CAS No. 7783-07-5)

Staff Scientist: NA
Chemical Manager: George Woodall, US EPA

George Woodall summarized the data set for hydrogen selenide (Attachment 15). He noted a minor discrepancy in the conversion calculation of ppm to mg/m^3. After presenting a brief history of the document, different methods for revising the current AEGL values were presented and discussed. 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. For derivation of AEGL-3 values, key studies were conducted in the same laboratory using the same protocol, equipment, species/strain (Zwart and Arts, 1989; Zwart et al., 1992). The value of *n* (*n*=2) was derived using combined data from Zwart and Arts (1989) and Zwart et al. (1992). However, this value does not appear correct, as results using *n*=2 are in conflict with empirical data. The Committee discussed how to classify animals that were described as morbid or killed in extremis. The Committee also discussed the appropriateness of combining these studies and basing the decision on the more conservative level that supports the data. George Woodall presented five approaches for deriving AEGL values: (1) use all available data and combine into a single analysis, with *n*=2.6 and a 60-minute LC_{01} = 33 ppm as POD; (2) use only data from the Zwart et al. (1992) study, with *n*=1.98 and a 60-minute LC_{01} = 29 ppm as POD; (3) use data from Zwart and Arts (1989) to derive a 60-minute LC_{01} = 66 ppm as POD; (4) use all 1-hour exposure data to derive a 60-minute LC_{01} = 67 ppm as POD; and (5) use re-scored data from Zwart et al. (1992) counting morbidly severe weight loss during the 2-week post-exposure observation period as mortality to derive a 60-minute LC_{01} = 10 ppm as POD.

George Woodall motioned, seconded by Bob Benson, that all data be used to determine the POD for AEGL-3 derivation, using a POD of 33 ppm and *n*=2.6 for AEGL-3 values of 10-minute: 2.2 ppm; 30-minute: 1.4 ppm; 1-hour: 1.1 ppm; 4-hour: 0.65 ppm; and 8-hour: 0.49 ppm.

For AEGL-2 values, all data showing weight loss and mortality would be used as the basis of the AEGL-2 values. These values would be approximate AEGL-2 values derived by taking one-third of AEGL-3 values, but would base the values on empirical data observations. Using a POD of 10 ppm and *n*=2.6, AEGL-2 values are 10-minute: 0.66 ppm; 30-minute: 0.44 ppm; 1-hour: 0.33 ppm; 4-hour: 0.20 ppm; and 8-hour: 0.15 ppm. In AEGL-2 values are consistent with observations of workers who showed severe irritation at the exposure level of 1.5 ppm, which supports that these levels also would be associated with the definition of an AEGL-2 of some irritation. The motion passed. (Appendix I: Yes: 15; No: 0; Abstain: 5)

AEGL Values for Hydrogen Selenide						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoints (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Inadequate data.
AEGL-2 (Disabling)	0.66 ppm (2.19 mg/m^3)	0.44 ppm (1.46 mg/m^3)	0.33 ppm (1.09 mg/m^3)	0.20 ppm (0.66 mg/m^3)	0.15 ppm (0.50 mg/m^3)	Weight loss and mortality; 10 ppm is POD; *n*=2.6; observation of workers who did not show irritation at the exposure level of 1.5 ppm.
AEGL-3 (Lethal)	2.2 ppm (7.29 mg/m^3)	1.4 ppm (4.64 mg/m^3)	1.1 ppm (3.64 mg/m^3)	0.65 ppm (2.15 mg/m^3)	0.49 ppm (1.69 mg/m^3)	POD of 33 ppm.

SPECIAL PRESENTATIONS

Discussion of Ethical Considerations of CO_2 Studies in Humans

Presenter: Iris Camacho, US EPA

Iris Camacho presented the background of the use of the EPA's role in supporting regulatory action under pesticide law, and the rules that have been issued to enhance the protection of humans in research. In the current NAS report entitled *Intentional human dosing studies for all EPA regulatory purposes*, it is stated that EPA should accept valid scientific studies unless there is clear evidence that there is action considered fundamentally unethical (i.e., harm being done to the subjects). These standards require formal reviews of any new chemicals for the AEGL Program. For the formal review, Iris is using the standards from the AEGL Standard Operating Procedure, and the recommendations from the NAS report to validate the studies that are being used with regards to CO_2.

Three studies involving inhalation exposure to CO_2 were evaluated for ethical validity. Two studies were from Vanderbilt University, and included informed consent, as well as approval from the local ethics Committee in which the protocol was deemed acceptable. It was concluded that there was no intention of harm (i.e., exposure levels were not deemed high enough to have lasting effects) and the study authors were looking at perception and response. After a discussion, John Hinz motioned, seconded by Rick Niemeier that the Committee feels that these studies were conducted under ethical considerations at that time. Motion has carried. (Appendix J: Yes: 19; No: 0; Abstain: 5)

The third study Glatee et al. (1967) was conducted with servicemen characterized as being volunteers, but there was not an environmental or ethical review. Concern for the validity of how the study was performed was noted by Alan Becker. After reviewing the data, the Committee considered the exposure as not high enough to impair bodily effects, and John Hinz made the motion and it was seconded by Marc Baril that the Committee had considered that the study and found that it did not pose a threat to the well-being of the participants of the study (i.e., pressure to volunteer, high exposure concentrations). The motion has carried. (Appendix J: Yes 18; No: 1; Abstain: 5)

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

LIST OF ATTACHMENTS

LIST OF APPENDICES