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

September 9-11, 2009

Meeting-49 Highlights

EPA-RTP Auditorium (Room C111-A&B)
U.S. EPA
109 TW Alexander Drive
Research Triangle Park, NC 27711

INTRODUCTION

Chairman George Rusch opened the meeting by calling for an introduction of all committee members and guests. R. Julian Preston, Associate Director for Health, NHEERL, welcomed the group and provided a brief overview of the U.S. EPA Research Triangle Park facility.

The draft NAC/AEGL-48 meeting highlights were reviewed. A motion to accept the minutes as written was made by Bob Benson (second by David Freshwater) and passed unanimously (Appendix A). The Final NAC/AEGL-48 meeting highlights are included as Appendix B.

Ernie Falke announced that NAS/COT meeting 19 would be held in October, 2009, in Amsterdam, The Netherlands. Sixteen chemicals, including Jet Fuel, are on the agenda for this meeting. NAS AEGLs Volume 7 has been published and should have been distributed to NAC members, and a pre-publication version of NAS AEGLs Volume 8 is scheduled for release in September, 2009. The interim report from NAS/COT meeting 18 (May, 2008) has just been received by the AEGL Program.

Ernie Falke provided an update on the status of the Agent VX TSD in consideration of new data. A more thorough overview may be presented at the next NAC meeting to provide a balanced discussion between the NAC and Douglas Summerville, U.S.Army ECBC.

Ernie Falke announced that this meeting will be the last official NAC meeting for the Oak Ridge National Laboratory staff. A new contractor should be in place by NAC-50. Continuity issue concerns were expressed by several committee members.

Paul Tobin informed the NAC that the 12th Federal Notice containing 19 chemicals had been published. Any comments received will be discussed at NAC-50. Paul also introduced new NAC members: Neeraja Erraguntla (Texas), Mattias Oberg (Sweden), Richard Erickson (U.S. Navy), and Clarion Johnson (Exxon-Mobil).

The highlights of the NAC/AEGL-49 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 REVISITS/STATUS UPDATES

Ricin (CAS No. 9009-86-3)

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

Bob Young informed the NAC that additional information regarding the new ricin data (Gomez et al., 2009) presented in a poster session at the Society of Toxicology meeting in March, 2009, had not yet been obtained. These 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. Further discussion of this chemical will be postponed until a published report if the Gomez data becomes available.

Lead (CAS No. 7439-92-1)

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

Jennifer Rayner reviewed the sparse data set for lead (Attachment 3) and informed the NAC that data appear to be insufficient for derivation of AEGL values. George Woodall suggested that the NCEA staff conducting the ambient guideline reassessment may be a source of information. This chemical was put in holding status until appropriate data may be obtained.

Dichlorvos (CAS No. 62-73-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: John Hinz, U.S. Air Force

Jennifer Rayner provided a review of the available data and currently proposed AEGL values (balloted at NAC-47) (Attachment 4). Jennifer then presented data from a recently obtained study

(MacDonald, 1982). After discussion (including vapor pressure, dose response, evaluation of whether to use as a key or supporting study) of the data from the MacDonald (1982) report, the committee chose not to use these data as a key or supporting study because of discrepancies in the data. The proposed AEGL values for dichlorvos were not revised and were considered to be protective of the population.

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

Staff Scientist: Carol Wood, ORNL
Chemical Manager: Ernie Falke, U.S. EPA

Ernie Falke presented information (Zwart et al., 1989; 1992) concerning the derivation of the time scaling exponent 'n' for hydrogen selenide. Currently, an n of 2 is utilized; however, data may suggest that an n of 1 may be more appropriate. Extrapolation from the rat 1-hr LC_{01} of 66 ppm to 2 hours using an n of 2 to estimate the 2 hour LC_{01} yields a value of 47 ppm; this concentration is above the threshold for lethality at 2 hours (1/2 died at 40 ppm). This calls into question the derivation of n. Given the sparse of data used to derive n and the fact that the n of 2 does not predict what is expected at 2 hours, it may be reasonable to change the n to 1 (default). After discussion, the NAC decided maintain the value of n=2 because this n value was derived using methods consistent with the SOP. Furthermore, the resulting AEGL values are not meaningfully different. George Woodall, Marcel van Raaij, and Ernie Falke agreed to look at different ways to analyze the Zwart data as it applies to the C x t protocol.

REVIEW of PRIORITY CHEMICALS

Dimethyl Phosphite (CAS No. 868-85-9)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for dimethyl phosphite (Attachment 5). AEGL-1 values were not proposed due to insufficient data. Proposed AEGL-2 values were based on clinical signs (labored breathing and ptosis) in mice exposed to 1575 ppm DMP for 6 hours (Hazleton, 1962). Inter- and intraspecies uncertainty factors of 3 each (total 10) were proposed because DMP is irritating, 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 between species or among individuals. The interspecies uncertainty factor of 3 was also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours. A modifying factor of 3 was also applied because of the sparse

database and because the point-of-departure is a nominal concentration. Temporal scaling 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 30-minute AEGL-2 value was adopted as the 10-min value because of the added uncertainty of extrapolating from the 6-hr point-of-departure.

Two sets of AEGL-3 values were proposed. The first used the same point-of-departure, uncertainty factors and time scaling as used in the derivation of AEGL-2 values. However, no uncertainty factor was applied because the effects noted at the POD were below those defined by AEGL-3. The highest concentration causing no mortality in rats (843 ppm for 6 hr) was used as the point-of-departure for the second approach (Biodymanics, 1980a). Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days. Death was noted at the next concentration tested (934 ppm) essentially after one exposure because one rat was killed *in extremis* after day 1 of the study. Uncertainty factor application and time scaling are as described for AEGL-2. No MF was applied.

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 dimethyl phosphite. The motion passed. (Appendix C: 20 yes; 0 no; 0 abstain).

Summary of AEGL Values for Dimethyl Phosphite						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)	Labored breathing and ptosis in mice (Hazleton, 1962)
AEGL-3 (Lethal)	190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (240 mg/m^3)	NOEL for mortality in rats (Biodynamics, 1980a)

NR: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

Trimethyl Phosphite (CAS No. 121-45-9)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Cheryl Bast presented a summary of the available data and an overview of the development of proposed AEGL values for trimethyl phosphite (Attachment 6). The no-effect-level for clinical signs in rats (10 ppm) exposed to TMP 6 hr/day, 5 days/week for 4 weeks (Biodynamics, 1979) was

used as the point-of-departure for AEGL-1 values. An intraspecies uncertainty factor of 3 was applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. An interspecies uncertainty factor of 1 was applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human occupational exposure data (AEGL-1 values derived with a total UF of 10 are 3.3, 2.3, 1.8, 1.1, and 0.60 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). Temporal scaling 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). Extrapolation was used to derive the 10-minute value because the 6-hour point-of-departure is from a repeated exposure study.

The lens opacities in rats exposed to 101 ppm TMP 6 hours/day, 5 days/week for 4 weeks (Biodynamics, 1979) were used as the point-of-departure for AEGL-2 values. This endpoint was still present in some animals at 2-weeks post-exposure. An intraspecies uncertainty factor of 3 was applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. The lens opacities observed in rats repeatedly exposed to 101 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure, suggesting a cumulative effect. An interspecies uncertainty factor of 1 was applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). Time scaling is as described above for AEGL-1.

Up to 50% lethality was observed in mice exposed to 6450 ppm TMP for approximately 3 hours (Hazleton, 1962). In the absence of other appropriate data for deriving AEGL-3 values, this exposure concentration was divided by 3 to estimate a threshold for lethality (point-of-departure 2150 ppm). Inter- and intraspecies uncertainty factors of 3 each (total 10) were applied because TMP is highly irritating, and much of the toxicity resulting from an acute exposure is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. Temporal scaling 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).

A motion was made by Bob Benson and seconded by Rick Niemeier to accept the AEGL-1, AEGL-2, and AEGL-3 values as proposed for trimethyl phosphite. The motion passed. (Appendix D: AEGL-1: 19 yes; 0 no; 1 abstain; AEGL-2 and AEGL-3: 20 yes; 0 no; 0 abstain).

Summary of AEGL Values for Trimethyl Phosphite						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)	NOEL for clinical signs in rats (Biodynamics,

						1979)
AEGL-2 (Disabling)	110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)	Lens opacities in rats (Biodynamics, 1979)
AEGL-3 (Lethal)	560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)	Estimated 3-hr lethality threshold in mice (Hazleton, 1962)

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

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

Sylvia Talmage reviewed the history of the methyl iodide technical support document (Attachment 7). The document presented at NAC-44 in December 2007 was put on hold until data on the effect of excessive iodide/iodine intake in pregnant women could be clarified. The document presented at NAC-46 in December 2008 was put on hold until results of modeling studies with the adult rat and fetal rabbit were published. Although the modeling studies were not directly used to derive AEGL values for methyl iodide, the studies did identify effects and mode of action for the various effects. Effects and mode of action for AEGL-relevant endpoints were: (1) lesions of the nasal passages in rats – glutathione depletion in nasal tissue and (2) neurotoxicity – effect of the circulating parent compound on nerve cells. Toxicity of iodide to the rabbit fetus was not used as a point of departure because iodide uptake is regulated in the human fetus whereas in the rabbit fetus it is not. Unregulated iodide uptake by the rabbit fetus leads to late fetal resorptions.

A weight-of evidence-approach was used to establish a point of departure for the AEGL-1. All data pertained to the rat. Both nasal lesions and neurotoxicity were addressed by the following relevant data: 27 ppm for 6 hours was a NOAEL for neurotoxicity (U.S. EPA 2006); 100 ppm for 1 hour was a NOAEL for nasal lesions (Reed et al. 1995); 100 ppm for 6 hours was a NOAEL for effect on breathing rate (DeLorme et al. 2009); 25 ppm was a 4-week NOAEL for nasal lesions and neurotoxicity (Monsanto et al. 1983); and 21 ppm was a subchronic NOAEL for nasal lesions and other effects (U.S. EPA 2006). The actual point of departure, 27 ppm for 6 hours, was divided by uncertainty factors of 1 (uptake is greater in the rat than humans based on a higher blood:air partition coefficient for methyl iodide) and 3 (metabolism by glutathione is not expected to differ greatly among humans) for a total of 3 (27 ppm/3 = 9 ppm). The 6-hour 9 ppm value was time scaled (C^n x t = k) with an n value of 2. The time-scaling factor was derived from several rat lethality data sets using the ten Berge log-probit model. In light of the no-effect value of 21 ppm in a subchronic study, the 8-hour AEGL-1 value was set equal to the 4-hour value.

The point of departure for the AEGL-2 was the 6-hour exposure to 100 ppm which resulted in reversible nasal lesions in the rat (Reed et al. 1995). Uncertainty factors and time scaling were the same as for the AEGL-1 above.

The lethality data sets of Eastman Kodak (1987), U.S. EPA (2006), and Reed et al. (1995) were entered into the ten Berge log probit model. The threshold for lethality was set at the lower limit of the 5% response (lower limit of the 95% confidence limit). The total uncertainty factor was 3. The program output automatically time-scaled the values (see table below). It was moved by Marcel van Raaij and seconded by George Woodall to accept the AEGL values. The motion passed (Appendix E: Yes: 19; No: 0; Abstain: 1).

Summary of AEGL Values for Methyl Iodide						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	54 ppm	31 ppm	22 ppm	11 ppm	11 ppm	NOAEL for neurotoxicity- rat (U.S. EPA 2006)
AEGL–2 (Disabling)	200 ppm	120 ppm	82 ppm	41 ppm	29 ppm	Reversible lesions of the nasal passages – rat (Reed et al. 1995)
AEGL–3 (Lethal)	670 ppm	400 ppm	290 ppm	150 ppm	98 ppm	Four lethality data sets for the rat entered into ten Berge log-probit model (5% response)

The derived values for methyl iodide were compared with the interim values for methyl chloride and methyl bromide. The AEGL values were consistent with relative toxicity as determined by LC_{50} values in the rat.

Phosgene (CAS No. 75-44-5)

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

At NAC-48, the committee voted to revise phosgene AEGL values published as final in Volume 2 to incorporate new data. Cheryl Bast reviewed the new data and revised derivations (Attachment 8). 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.

Appropriate data were not available for deriving AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 to 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious

effects may occur after a clinical latency period of 24 hours. Therefore, AEGL-1 values are not recommended.

The NOAEL for increased PMNs in BAL fluid observed in dogs (2.3 ppm for 30 minutes) (Pauluhn, 2006c) was used as the basis for deriving AEGL-2 values. The dog was chosen over rodents because, with regard physiology of the respiratory tract and acinar structure of the lung, dogs are more similar to humans than rodents. This endpoint was chosen because BAL fluid changes are a sensitive marker of phosgene-induced noncardiogenic pulmonary high-permeability edema following acute inhalation exposure (Pauluhn et al., 2007). An uncertainty factor of 1 was applied for interspecies extrapolation. In rats, c x t products of between 48 ppm·min and 60 ppm·min induced increased protein in BAL fluid , and no increase was noted from 24-30 ppm·min. In mice and hamsters, a C x t product of 48 ppm·min induced an increase of protein in BAL fluid, and no increase was noted at 24 ppm·min. However, in dogs, a C x t product of 129 ppm·min was necessary to cause an increase in protein in BAL fluid, and no increase was observed at 63 ppm·min. Thus, the CT product required to induce an increase in protein in BAL fluid in dogs is approximately two-fold greater than in rodents, and the NOAEL for increased BAL protein in dogs (63 ppm·min) is higher than the LOAEL values in rodents (48-60 ppm·min). Additionally, with regard to physiology of the respiratory tract and acinar structure of the lung, dogs are more similar to humans than rodents (Pauluhn, 2006a, 2006b, 2006c; Pauluhn et al., 2007). Collectively, these data suggest that an interspecies uncertainty factor of no more than 1 is justified when extrapolating from laboratory animals to humans. An uncertainty factor of 3 was applied to account for sensitive human subpopulations. The intraspecies UF of 3 is considered sufficient due to the steep concentration-response curve (death in 2/10 rats exposed to 52.3 ppm and 6/10 exposed to 61.9 ppm for 10 min; 4/10 exposed to 13.4 ppm and 10/10 exposed to 16.7 ppm for 30-min; 4/10 exposed to 7.4 ppm and 10/10 exposed to 11.8 ppm for 1-hr; Pauluhn, 2006a) which implies limited intra-individual variability. Also, the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. The concentration-time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). Haber's Law C x t = k; n=1 has been shown to be valid for phosgene within certain limits and will be used for scaling of the AEGL values for phosgene.

The AEGL-3 values were based on an estimated 1-hour lethality threshold of 3.9 ppm ($BMCL_{05}$) in rats (Pauluhn, 2006a). The duration of exposure in this study is expected to minimize inaccuracy in the estimated lethality threshold due to bradypnea in the rats. Uncertainty factor application and time scaling are as described above for derivation of AEGL-2 values.

It was moved by Bob Benson and seconded by Marc Baril to accept the AEGL values. The motion passed (Appendix F: AEGL-1 and AEGL-2: Yes: 20; No: 0; Abstain: 0; AEGL-3: Yes: 19; No: 0; Abstain: 1). Values are listed in the table below.

Summary of Proposed AEGL Values for Phosgene						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not Recommended
AEGL-2 (Disabling)	2.3 ppm (9.5 mg/m^3)	0.77 ppm (3.2 mg/m^3)	0.38 ppm (1.6 mg/m^3)	0.096 ppm (0.39 mg/m^3)	0.048 ppm (0.19 mg/m^3)	Increased PMNs in BAL fluid in dogs (Pauluhn, 2006c)
AEGL-3 (Lethal)	7.8 ppm (32 mg/m^3)	2.6 ppm (11 mg/m^3)	1.3 ppm (5.3 mg/m^3)	0.33 ppm (1.4 mg/m^3)	0.16 ppm (0.66 mg/m^3)	Estimated 1-hr lethality threshold ($BMCL_{05}$) in rats (Pauluhn, 2006a)

NR: Not Recommended. Absence of AEGL-1 values does not imply that exposure to concentrations below AEGL-2 are without effect.

Dicrotophos (CAS No. 141-66-2)

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

Dicrotophos was first discussed at NAC-47. At that meeting the NAC decided to defer action until the TSD for monocrotophos was available to allow the NAC to consider both chemicals together. Monocrotophos is the hydrolysis product of dichrotophos. Inhalation data in animals are limited to conflicting lethality data for rats, poorly characterized exposure-response data for nonlethal effects, and inadequate information on the exposure concentration-duration relationship. Sachsse et. al. (1974) reported both 1-hour and 4-hour LC_{50} values of 90 mg/m^3 for male and female rats exposed to dicrotophos (technical; 87.8% purity). AEGL-1 values for dicrotophos were not recommended due to insufficient data. Data were also insufficient to derive AEGL-2 values. The limited exposure-response data for rats, however, indicate that the exposure-response relationship for dicrotophos is steep; 480 mg/m^3 to 720 mg/^{3} for technical formulation and 810 mg/m^3 to 860 mg/m^3 for a 38% solution) for a 1-hour duration spanned a lethality rate from 0% up to 100%. Consistent with NRC (2001) guidelines, a 3-fold reduction of the AEGL-3 values would provide a justifiable estimate of the AEGL-2 values. The 1-hour LC_{50} value of 90 mg/m^3 reported by Sachsee et al. (1974) served as the initial point-of-departure (POD) for AEGL-3. This value was adjusted to 78.9 mg/m^3 to adjust for reported 87.7% purity of the test article. Due to the steep exposure-response relationship for dicrotophos, a lethality threshold of 26.3 mg/m^3 for rats was estimated by a 3-fold reduction of the 78.9 mg/m^3 LC_{50} value. Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). However, the variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE levels are greater in humans than in rodents, and human plasma ChE activity represents a greater portion of blood ChE activity relative to animal species. Furthermore, baseline RBC ChE activity is higher in humans relative to animal species which

provides an additional protective advantage. Therefore, the proposed interspecies uncertainty factor was limited to 3. The default intraspecies uncertainty factor of 10 was maintained for dicrotophos AEGL-3 values. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses. Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans. Individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase and these individuals may exhibit greater sensitivity to some anticholinesterase compounds. Evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans (summarized in NRC, 2003). In the absence of chemical-specific data showing that dicrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained. In the absence of definitive data to derive n, temporal scaling default exponents of $n = 3$ were applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001). John Hinz made the motion to accept the values as presented. Mark Baril seconded the motion. The motion passed (Appendix G: Y: 20; N: 0; Pass: 0).

AEGL Values for dicrotophos (mg/m^3)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	0.53	0.37	0.29	0.073	0.037	3-fold reduction of AEGL-3 values
AEGL-3 (Lethality)	1.6	1.1	0.88	0.22	0.11	Lethality threshold estimated as 3-fold reduction of 1-hr LC_{50} of 78.9 mg/m^3 (90 mg/m^3 reported adjusted for 87.7% purity of test article) ÷ 3 = 26.3 mg/m^3 in rats (Sachsse et al., 1974); UF=10x3

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Monocrotophos (CAS No. 6923-22-4)

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

Bob Young provided a review of the available data and draft AEGL values for monocrotophos (Attachment 9). Data are limited to LC_{50} studies for 1 and 4 hours duration of exposure. The 1 hour LC_{50} was 94 mg/m^{3}and the 4 hour LC_{50} was 80 mg/m^3. AEGL-1 values for monocrotophos were not recommended due to insufficient data. Data were also insufficient regarding effects consistent with AEGL-2 tier severity. No exposure-response data were available that identified effects consistent with AEGL-2 tier severity or that enabled an assessment of an exposure-response relationship. The available studies provided lethality benchmarks but no individual or exposure-specific response data. Although one study reported that typical cholinergic responses were observed in all exposure groups, the severity of the responses was not specified and it was unknown as to which, if any, of the exposures were without lethal responses. In the absence of data consistent with the AEGL-2 tier, the AEGL-2 values were estimated as a 3-fold reduction of the AEGL-3 values under the assumption that the exposure-response curve for monocrotophos was very steep like that of other organophosphates. The 1-hour LC_{50} of 94 mg/m^3 and 4-hour LC_{50} of 80 mg/m^3 (adjusted to 66.1 and 56.2 mg/m^3, respectively, to account for the 70.3% purity of the test article) for rats reported by Sachsse et al. (1974) were used as initial points-of-departure (POD) for derivation of AEGL-3 values. Lethality thresholds for these exposure durations were estimated as a 3-fold reduction of the adjusted 1-hr and 4-hr LC_{50} values; 22.0 mg/m^3 for 1-hour duration and 18.7 mg/m^3 for a 4-hour duration. Although data for monocrotophos are limited, this approach was justified by the fact that other organophosphates exhibit a steep exposure-response relationship, and it is assumed that monocrotophos having the same mode of action would likely exhibit a similar exposure-response relationship. The use of two duration-specific values within the AEGL duration span reflects the available data more than a default time scaling across the 10-minute to 8-hour time span. Uncertainty factor application is as described above for dicrotophos. The default procedure for time scaling was used (n = 3 or 1) as no data are available to derive a value of n. John Hinz made the motion to accept the values. Mark Baril seconded the motion. The motion passed (Appendix H: Yes: 20; No: 0; Abstain: 0).

AEGL Values for Monocrotophos (mg/m^3)						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	0.43	0.31	0.24	0.21	0.10	AEGL-2 values estimated by a one-third reduction of AEGL-3 values
AEGL-3 (Lethality)	1.3	0.92	0.73	0.62	0.31	lethality threshold estimated as a 3-fold reduction of 1-hour and 4-hour rat LC_{50} values of 66.1mg/m^3 and 56.2 mg/m^3 (adjusted for 70.3% purity from 94 and 80 mg/m^3) to 22.0 and 18.8 mg/m^3 respectively) (Sachsse et al., 1974); UF=3x10; $C^n x\ t = k$, where n=1 or 3

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Methamidophos (CAS No. 10265-92-6)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Henry Anderson, Wisconsin Department of Health

Data on the organophosphate pesticide, methamidophos, were presented by Sylvia Talmage (Attachment 10). All acute inhalation studies used the rat as the test species; methamidophos was administered as a liquid aerosol. Lethality data from two different laboratories, Sanga 1983; 1984 and Pauluhn 1986, did not agree. In both laboratories, nominal concentrations were several-fold higher than analytical concentrations, indicating that the aerosol atmosphere was difficult to maintain. The data of Pauluhn was chosen to derive values because it followed a better concentration-response curve, analytical concentrations correlated with nominal concentrations, and cholinesterase activity was measured. The committee rejected a 4-hour NOAEL for clinical signs of 11.4 mg/m^3 for the higher value of 24.3 mg/m^3, also a 4-hour NOAEL for clinical signs (Pauluhn 1986). Clinical signs were observed at the next higher concentration of 45.0 mg/m^3. At 24.3 mg/m^3, plasma cholinesterase activity was 36% of the control value and erythrocyte cholinesterase activity was 92% of the control value. Because of the disparity in the data between the two laboratories, the 24.3 mg/m^3 value was divided by a data base modifying factor of 2. Oral dosing studies showed rapid metabolism in both rats and humans. Therefore, an interspecies uncertainty factor of 3 was applied. Infants are believed to be the sensitive population regarding organophosphate toxicity. But, oral dosing studies of adult and juvenile rats failed to show that juveniles were more sensitive than adults. Therefore an intraspecies uncertainty factor of 3 was applied. The total modifying/uncertainty factor was 20 (2x10). In the absence of time-scaling data, the 4-hour value of 1.2 mg/m^3 was time-scaled to shorter and longer exposure durations using the default values of 1 and 3, respectively. Because the key study was 4 hours, the 10-minute AEGL-1 was set equal to the 30-minute value.

The 4-hour exposure of rats to 45.0 mg/m^3 in the study by Pauluhn (1986) was chosen as the point of departure for the AEGL-2. Clinical signs consisted of tremor, staggering, and reduced motility. Plasma and erythrocyte cholinesterase activity were 13 and 70% of control, respectively. Mortality of 30% occurred at the next higher exposure of 195.5 mg/m^3. The same modifying and uncertainty factors and time scaling were applied as for the AEGL-1 above.

The 4-hour exposures of rats to methamidophos delivered as a liquid aerosol at concentrations of 11.4 to 350.3 mg/m^3 in the study of Pauluhn (1986) were used to develop AEGL-3 values. The threshold for lethality was calculated using U.S. EPA's Benchmark Concentration (BMC) program (V2.8). The $BMCL_{05}$ was 56.27 mg/m^3, and the BMC_{01} was 101.54 mg/m^3. Although the lower value, in this case the $BMCL_{05}$ of 56.27 mg/m^3, is generally chosen as the threshold for mortality in developing AEGL-3 values, this value was considered an artifact of the large gap between tested concentrations of 45.0 and 195.5 mg/m^3. The 56.27 mg/m^3 value is also close to the 45.0 mg/m^3 value that resulted in effects considered consistent with the definition of AEGL-2. The 4-hour BMC_{01} of 101.54 mg/m^3 for methamidophos delivered as a liquid aerosol was considered the

threshold for mortality in rats. The same modifying and uncertainty factors and time scaling were applied as for the AEGL-1 and AEGL-2 above. It was moved by Henry Anderson and seconded by Rick Niemeier to accept the values as proposed. The motion passed (Appendix J Yes: 16; No 0: Abstain: 3).

Summary of AEGL Values for Methamidophos						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	2.4 mg/m^3	2.4 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	0.61 mg/m^3	No clinical signs – rat (Pauluhn 1986)
AEGL-2 (Disabling)	4.5 mg/m^3	4.5 mg/m^3	3.6 mg/m^3	2.3 mg/m^3	1.1 mg/m^3	Clinical signs of tremor, reduced motility – rat (Pauluhn 1986)
AEGL-3 (Lethal)	10 mg/m^3	10 mg/m^3	8.1 mg/m^3	5.1 mg/m^3	2.5 mg/m^3	4-hour $BMCL_{01}$ for lethality – rat (Pauluhn 1986)

Mevinphos (CAS No. 7786-34-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Daniel Sudakin, Oregon State University

Jennifer Rayner provided a review of the extremely sparse data set and draft AEGL values for mevinphos (Attachment 11). Only one study is available and data cannot be validated. After discussion, a motion was made by George Woodall and seconded by John Hinz to place mevinphos in holding status due to lack of data. If new data become available, mevinphos will be reevaluated. The motion passed. *(*Appendix J: 16 yes; 0 no; 4 abstain).

Phosphamidon (CAS No. 13171-21-6)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Ed Bernas, AFLCIO

Data on the organophosphate pesticide, phosphamidon, were presented by Sylvia Talmage (Attachment 12). All acute data originated in a single laboratory, and all acute data addressed lethality. 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 fact that dividing an LC_{50} value by 3 generally results in a non-lethal value (NRC 2001), the AEGL-2 values were calculated by dividing the AEGL-3 values by 3.

The 4-hour nose-only exposure of rats to phosphamidon at a concentration of 102 mg/m^3 (Sachsse et al. 1980) was selected as the point of departure for the AEGL-3. This value is the most conservative

of the three 4-hour LC_{50} values provided for the rat. Only the 4-hour LC_{50} value of 102 mg/m^3 was provided; tested concentrations were not reported. Because of the sparse data base and conflicting values reported for 1- and 4-hour exposures, the 4-hour LC_{50} value of 102 mg/m^3 was divided by a data base modifying factor of 2. In the absence of empirical data on a non-lethal concentration, a non-lethal concentration may be calculated by dividing the LC_{50} by 3 (Rusch et al. 2009). A larger divisor in conjunction with modifying and inter- and intraspecies uncertainty factors would reduce the 4-hour AEGL-3 value to less than the 0.5 mg/m^3 concentration tolerated by rats for 42 days (Battelle Institute 1965). An interspecies uncertainty factor of 3 was applied. Rats were more sensitive to the toxicity of phosphamidon than guinea pigs, but not as sensitive as mice. An intraspecies uncertainty factor of 10 was applied because there is little information regarding metabolism differences among humans. The total modifying/uncertainty factor is 60 (2x3x10). The resulting 4-hour value of 0.57 mg/m^3 was time-scaled ($C^n \times t = k$) from the 4-hour data point using n values of 3 and 1 for extrapolation to shorter and longer exposure duration, respectively. Because the key study was 4 hours, the 10-minute value was set equal to the 30-minute value. It was moved by Bob Benson and seconded by Susan Ripple to accept the values (listed in the table below). The motion passed (Appendix K: Yes: 16; No 1: Abstain: 3).

Summary of AEGL Values for Phosphamidon						
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)	0.37 mg/m^3	0.37 mg/m^3	0.30 mg/m^3	0.19 mg/m^3	0.093 mg/m^3	One-third of the AEGL-3 values
AEGL-3 (Lethal)	1.1 mg/m^3	1.1 mg/m^3	0.90 mg/m^3	0.57 mg/m^3	0.28 mg/m^3	4-hour LC_{50} for lethality divided by 3 – rat (Sachsse et al. 1980)

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

Fenamiphos (CAS No. 22224-92-1)

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

Data on fenamiphos were presented by Jennifer Rayner (Attachment 13). No AEGL-1 values were proposed because the derived AEGL-1 values were too close to or exceeded AEGL-2 values. The AEGL-2 was derived by dividing the AEGL-3 by three due to lack of experimental data and the steep exposure-response relationship observed. Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour, 30% mortality at 87 mg/m^3, and 60% mortality at103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour, 60% died after exposure to 145 mg/m^3, and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90%

mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 100 mg/m^3 and 100% mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3 90% mortality at 155 mg/m^3, and 100% mortality at 191 mg/m^3. The lack of experimental data and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC 2001). The AEGL-3 was derived using the $BMCL_{05}$ of 46.6337 mg/m^3 for lethality in female rats exposed for 4 hours to fenamiphos (Thyssen 1979a). Lethality data were sufficient for empirical derivation of a time-scaling factor (*n*) for use in the equation $C^n \times t = k$. The value of n was 4.8 and was used to time scale AEGL values. The mechanism of action of organophosphate anticholinesterases is well understood and their activity on cholinergic systems is the same across species. Variability in response is primarily a function of varying cholinesterase activities and types of cholinesterase. Humans have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as fenamiphos, thereby decreasing the availability of the compound to brain cholinesterase. Therefore, the interspecies uncertainty factor is limited to 3. The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10. The uncertainty factor application and rationale are the same as those applied in the derivation of AEGLs for other organophosphate anticholinesterases (NRC 2003).

A motion was made by John Hinz and seconded by Rick Niemeier to accept the values as presented. The motion passed (Appendix L: 19 yes; 0 no; 0 abstain).

Summary of AEGL Values for Fenamiphos						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to exceeding AEGL-2 values
AEGL-2 (Disabling)	1.0 mg/m^3	0.80 mg/m^3	0.70 mg/m^3	0.53 mg/m^3	0.43 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC 2001; Thyssen 1979a)
AEGL-3 (Lethal)	3.0 mg/m^3	2.4 mg/m^3	2.1 mg/m^3	1.6 mg/m^3	1.3 mg/m^3	Derived based upon a 4-hr $BMCL_{05}$ of 46.6337 mg/m^3 in rats (Thyssen 1979a)

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Automotive Gasoline (CAS No. 86290-81-5; 8006-61-9)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: John Hinz, U.S. Air Force

John Hinz provided background information and the approach for derivation of AEGL values for AEGL-49

automotive gasoline vapor. Where data were available, values were based on wholly vaporized gasoline. Sylvia Talmage addressed calculation of the values (Attachment 14). The data base for gasoline vapor is rich. Clinical studies addressed irritation and central nervous system depression. Rodent studies addressed general toxicity, neurotoxicity, reproductive and developmental toxicity, genetic toxicity, and chronic toxicity/carcinogenicity. The AEGL-1 was based on the sensory irritation study of Davis et al. (1960) in which volunteers were exposed to three different blends of gasoline vapor. Each blend was tested at approximately 880, 2200, and 4400 mg/m^3 for 30 minutes. Because of increased ocular tearing, the suggested point of departure for the AEGL-1 of 4400 mg/m^3 was rejected in favor of the 2200 mg/m^3 value. The 30-minute exposure to all three blends of gasoline vapor at 2200 mg/m^3 produced subjective eye irritation at a higher incidence (15/30 subjects) than under control conditions (1/20 subjects). The incidence of objective eye irritation, observed photographically, although scored as slight (+1 on a scale of 1 to 4), was higher in the 2200 mg/m^3 group (15/30) than in the control group (2/20). Incidences of ocular tearing were similar in this group (3/30) and the control group (2/20). Incidences of subjective and objective eye irritation were greater at the higher concentration of 4400 mg/m^3. Because the eye irritation when measured objectively was slight (less than marked), an intraspecies uncertainty factor of 3 was applied to protect sensitive subjects. There is adaptation to the slight irritation that defines the AEGL-1. Therefore, the same value of 730 mg/m^3 (2200 mg/m^3/3) was used across all exposure durations.

Tested concentrations in rodent studies of acute duration were not high enough to induce narcotic effects. The acute studies were conducted for 4 hours at the limit concentration of 5000 mg/m^3. The AEGL-2 values were based on the subchronic study of Schreiner et al. (2000) in which male and female Sprague-Dawley rats inhaled 22,500 mg/m^3 gasoline vapor (whole-body) for 6 hours/day, 5 days/week for 13 weeks. The rats failed to show clinical signs indicative of neurotoxicity during exposure. The point of departure, the 6-hour exposure to 22,500 mg/m^3, was divided by interspecies and intraspecies uncertainty factors of 1 and 3, respectively for a total uncertainty factor of 3. An interspecies uncertainty factor of 1 is sufficient because solvent uptake is generally greater in rodents than in humans based on higher blood:air partition coefficients for several hydrocarbons. Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to central nervous system depressants varies by no more than 2- to 3-fold as indicated by the minimum alveolar concentration, the concentration of an anesthetic that produces immobility in 50% of patients. Therefore, an intraspecies uncertainty factor of 3 is sufficient. Higher uncertainty factors would result in values inconsistent with the clinical study of Davis et al. (1960). Time scaling may not be relevant for hydrocarbons that act as anesthetics as blood concentrations of the major light components of gasoline rapidly approach steady-state. Therefore, the 6-hour value of 7500 mg/m^3 (22,500 mg/m^3/3) was used across all exposure durations. The 7500 mg/m^3 value is supported by the study of Kuna and Ulrich (1984) in which no toxic signs were observed in squirrel monkeys exposed to 6350 mg/m^3 for six hours/day for 13 weeks.

None of the concentrations tested in acute or subchronic studies with rodents resulted in mortality. It is not apparent that concentrations high enough to cause death from inhalation of gasoline vapor can be attained. Based on the likelihood that lethal concentrations of gasoline vapor cannot be attained/sustained under ambient conditions, an AEGL-3 was not determined.

A motion was made by Henry Anderson and seconded by Bob Benson to accept the values. The motion passed (Appendix M: 20 yes; 0 no; 0 abstain).

Summary of AEGL Values for Automotive Gasoline Vapor						
Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	Slight eye irritation in humans (Davis et al. 1960)
AEGL-2 (Disabling)	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	No clinical signs at highest tested concentration of 22,500 mg/m^3 – rat (Schreiner et al. 2000)
AEGL-3 (Lethal)	Not determined	Not determined	Not determined	Not determined	Not determined	No data**

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.
**A lethal concentration was not attained in the available acute, subchronic, and chronic toxicity studies.

Cadmium (CAS No. 7740-43-9)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Jennifer Rayner reviewed the data set and draft AEGL values for cadmium (Attachment 15). The AEGL-1 values are based on the experimental concentration, 0.55 mg Cd/m^3, that caused slight respiratory irritation in rats (Takenaka et al. 2004). After a 6 hour exposure, increased neutrophils and multifocal alveolar inflammation were observed. At the next higher experimental exposure, pneumonitis was observed (Grose et al. 1987). Although the exposure was a whole-body exposure, the size of the ultrafine particles (51 nM MMAD, 1.7 GSD) would mimic a gaseous state and the majority of the aerosol would be inhaled and not deposited on the fur. An intraspecies uncertainty factor of 3 was applied because at acute exposures, cadmium is a direct-acting respiratory irritant. Rabbits and rats exposed to cadmium from 1-6 hours exhibited pneumonitis, increased lung weight, and pulmonary inflammatory cell influx. This mode of action is not expected to differ among species. Human data suggested that cadmium is a direct-acting irritant following acute exposures. After a five hour exposure to cadmium, workers experienced cough, throat irritation, dyspnea, and pulmonary edema (Beton et al. 1966). Therefore, an intraspecies UF of 3 was applied. This mode of action is not expected to differ among individuals. In the absence of an empirically derived chemical-specific scaling exponent, temporal scaling 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. The 30-minute AEGL-1 value was adopted as the 10-minute value due to the added uncertainty of extrapolating from a 6-hour time point to 10 minutes (NRC 2001). The AEGL-2

values are based on the experimental concentration, 5.3 mg Cd/m^3, that caused overt respiratory irritation and pathology in rats (Buckley and Bassett 1987). The 3 hour exposure resulted in reduced weight gain and increased lung weight, protein content, DNA content, number of cuboidal alveolar cells, number of inflammatory cells, and focal areas of interstitial thickening. Uncertainty factor application and time scaling are as described for AEGL-1. The AEGL-3 values are based on the 2 hour LC_{50} for cadmium fume in rats, 112 mg/m^3 (Rusch et al. 1986). The LC_{50} was divided by 3 to estimate a threshold of lethality. Uncertainty factor application and time scaling are as described for AEGL-1.

Motions were made to accept AEGL-1 (motion: Bob Benson; second: John Hinz), AEGL-2 (motion: Marcel van Raaij; second: Bob Benson), and AEGL-3 (motion: Marc Baril; second: Bob Benson) values as proposed. The motions passed (Appendix N: 17 yes; 0 no; 0 abstain).

Summary of AEGL Values Cadmium						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	0.13 mg/m^3	0.13 mg/m^3	0.10 mg/m^3	0.063 mg/m^3	0.041 mg/m^3	Respiratory irritation, 0.55 mg Cd/m^3 for 6 hr (Takenaka et al. 2004)
AEGL-2 (Disabling)	1.4 mg/m^3	0.96 mg/m^3	0.76 mg/m^3	0.40 mg/m^3	0.20 mg/m^3	Overt respiratory tract irritation and pathology, 5.3 mg/m^3 CdO for 3 hr (Buckley and Bassett.1987)
AEGL-3 (Lethal)	8.5 mg/m^3	5.9 mg/m^3	4.7 mg/m^3	1.9 mg/m^3	0.93 mg/m^3	Threshold of lethality based on the 2-hr rat LC_{50} for Cd fumes, 112 mg/m^3 (Rusch et al. 1986)

Red Phosphorus (CAS No. 7723-14-0)

Staff Scientist: Robert Young, ORNL
Chemical Manager: Glenn Leach, U.S. Army

Bob Young reviewed the data set and draft AEGL values for red phosphorus (Attachment 16). Data were unavailable with which to directly derive AEGL-1 values for red phosphorus. A 3-fold reduction of the AEGL-2 values was considered a justified approach for deriving the AEGL-1 values because the progression of effects from AEGL-1 severity to AEGL-2 severity represents a continuum of the same mode of action (contact irritation) and effect. Comparison of the AEGL-1 values to the limited human exposure data indicates that notable effects (greater than those characterizing the AEGL-1 tier) would be unlikely following exposure to AEGL-1 concentrations. Information regarding the response of humans to red phosphorus or red phosphorus/butyl rubber

smoke lacked definitive exposure terms and was not considered sufficient for development of AEGL-2 values. The AEGL-2 severity effects in animals (necrosis, hemorrhage, and edema in the respiratory tract) were consistently associated with exposures that also caused deaths. Necropsies of animals surviving through the post-exposure observation period generally revealed only minor signs of toxicity that were not consistent with AEGL-2 severity but clearly showed the respiratory tract as a target of toxicity. Results from the multispecies study by Ballantyne (1998), showed no lethality and only pulmonary congestion in mice exposed one hour to smoke of unformulated red phosphorus (111 mg/m^3). The data reported by Ballantyne (1998) were also considered the most relevant for deriving AEGL values for red phosphorus because pure unformulated red phosphorus was used rather than the butyl rubber formulations. Mice appeared to be more sensitive than rabbits, dogs, or rats. The 1-hour exposure of mice to 111 mg red phosphorus/m^3 that resulted in pulmonary congestion was considered an appropriate point-of-departure (POD) for AEGL-2 derivation with a total uncertainty factor application of 10 (3 for intraspecies variability and 3 for interspecies variability). Red phosphorus is a direct-contact irritant which is primarily due to the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics which justifies an intraspecies uncertainty factor of 3. Because the mouse appeared to be a sensitive species and the critical effect associated with the POD are of minimal severity for the AEGL-2 tier, the interspecies uncertainty factor of 3 is considered adequate. Further reduction of the AEGL-2 values by additional uncertainty adjustment would result in AEGL-2 values inconsistent with the limited information available for humans. In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs 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). For AEGL-3 development, human data lacked definitive exposure terms but served as supporting data. As for AEGL-2, the Ballantyne (1998) study was considered more relevant for deriving AEGL values for red phosphorus due to its use of pure unformulated red phosphorus rather than the butyl rubber formulations. The 1-hour $BMLC_{05}$ of 469 mg/m^3 for rats exposed to red phosphorus smoke was used as the POD for AEGL-3 derivation. Although results of the Ballantyne (1998) study indicated the mouse is a more sensitive species, the BMC analyses of the mouse data showed the BMC model to be a poor fit (p=0.09 for the mouse data vs p=0.66 for the rat data). Furthermore, overall data in rats are more robust. The lethality benchmark values from the Ballantyne data are lower than those from other studies. Animal lethality data exhibited considerable variability that would normally warrant an interspecies uncertainty factor of 10. However, this would result in AEGL-3 values inconsistent with human occupational data. The interspecies variability is primarily the result of the extreme sensitivity of guinea pigs which the investigators and the NRC (1997a) considered uniquely susceptible and inappropriate for human health risk assessment. Therefore, the interspecies uncertainty factor was limited to 3. Red phosphorus is a direct-contact irritant which is a function of the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus was considered a greater determinant of the toxic response than toxicokinetics, thereby justifying an intraspecies uncertainty factor of 3. As previously noted, greater uncertainty application would result in AEGL-3 values inconsistent with the human experience data. Time scaling was performed as described for AEGL-2. A motion was made by Bob Benson and seconded by John Hinz to accept the values. The motion passed

(Appendix O: AEGL-1: 14 yes; 1 no; 4 abstain; AEGL-2: 16 yes; 1 no; 2 abstain; AEGL-3: 16 yes; 0 no; 3 abstain).

AEGL Values For Red Phosphorus (mg/m^3)						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	6.7	4.7	3.7	0.93	0.47	3-fold reduction of the AEGL-2 values as a protective estimate of AEGL-1 severity
AEGL-2 (Disabling)	20	14	11	2.8	1.4	Mild pulmonary congestion in mice; 1-hr exposure to 111 mg/m^3 (Ballantyne, 1998); UF= 3 x 3; n=1 or 3
AEGL-3 (Lethality)	85	59	47	12	5.9	Rat 1-hr $BMCL_{05}$ of 469 mg/m^3 (Ballantyne, 1998); UF= 3 x 3; n=1 or 3

SPECIAL PRESENTATIONS

Organophosphate (OP) Pesticide Uncertainty Factors

A general discussion of OP uncertainty factors was led by Jennifer Rayner and Ernie Falke (Attachment 17). The NAC is preparing several TSDs for OP pesticides and there is a need to better justify uncertainty factors. Bob Young is preparing a white paper to address OP uncertainty factor issues to determine if chemical class generalizations may be valid for the OP pesticides. However, it is possible that data may not be sufficient to support OP chemical-class uncertainty factors; thus, chemical-specific uncertainty factors and justifications could be necessary. Ernie Falke, George Woodall, and Bob Benson volunteered to serve on an OP working group.

Discussion of Benchmark Software

Presenters: Allen Davis and Jeffrey Gift, U.S. EPA

Allen Davis and Jeff Gift presented information on the most recent version of the benchmark software (BMDS 2.1) (Attachment 18). The presentation focused on use of the program, c x t modeling, and selection of appropriate models.

ADMINISTRATIVE MATTERS

Future Meetings:
April 13-15, 2010: San Francisco, CA

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 49 agenda
Attachment 2. Meeting 49 attendee list
Attachment 3. Lead presentation
Attachment 4. Dichlorvos presentation
Attachment 5. Dimethyl phosphite presentation
Attachment 6. Trimethyl phosphite presentation
Attachment 7. Methyl iodide presentation
Attachment 8. Phosgene presentation
Attachment 9. Monocrotophos presentation
Attachment 10. Methamidophos presentation
Attachment 11. Mevinphos presentation
Attachment 12. Phosphamidon presentation
Attachment 13. Fenamiphos presentation
Attachment 14. Gasoline presentation
Attachment 15. Cadmium presentation
Attachment 16. Red phosphorus presentation
Attachment 17. OP Uncertainty factor presentation
Attachment 18. BMDS presentation
Attachment 19. NAC- 49 meeting certification

LIST OF APPENDICES

Appendix A. Ballot for approval of NAC-48 meeting highlights
Appendix B. Final NAC-48 Meeting Highlights
Appendix C. Ballot for dimethyl phosphite
Appendix D. Ballot for trimethyl phosphite
Appendix E. Ballot for methyl iodide
Appendix F. Ballot for phosgene
Appendix G. Ballot for dicrotophos
Appendix H. Ballot for monocrotophos
Appendix I. Ballot for methamidophos
Appendix J. Ballot for mevinphos
Appendix K. Ballot for phosphamidon
Appendix L. Ballot for fenamiphos
Appendix M. Ballot for gasoline
Appendix N. Ballot for cadmium
Appendix O. Ballot for red phosphorus

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-49
September 9-11, 2009

ATTACHMENT 1

EPA-RTP Auditorium (Room C111-A&B)
U.S. EPA
109 TW Alexander Drive
Research Triangle Park, NC 27711

AGENDA

Wednesday, September 9, 2009

10:00 a.m.	*Development team meetings: Cadmium, Gasoline, Red phosphorus, Dimethyl phosphite, trimethyl phosphite)
11:00	Welcome (R. Julian Preston, Associate Director for Health, NHEERL, U.S. EPA)
11:15	Introductory remarks and approval of NAC/AEGL-48 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:30	Ricin Update (Jim Holler/Bob Young)
11:35	Lead- Status Update and Review of potential approaches (George Woodall/Jennifer Rayner)
12:00 p.m.	Lunch
1:00	Review of Dimethyl Phosphite (George Cushmac/Cheryl Bast)
1:30	Review of Trimethyl Phosphite (George Cushmac/Cheryl Bast)
2:00	Revisit of Methyl iodide (Alan Becker/Sylvia Talmage)
3:00	Break
3:15	Revisit of Phosgene- New data (Ernie Falke/Cheryl Bast)
4:15	Benchmark Software Presentation (Allen Davis/ Jeff Gift)
5:15	Administrative matters
5:30	Adjourn for the day

Thursday, September 10, 2009

8:30 a.m.	*Development team meetings: Organophosphate Pesticides (Dichlorvos, Dicrotphos, Fenamiphos, Methamidophos, Mevinphos, Monocrotophos, Phosphamidon)
9:30	Review of Dichlorvos (AEGL-3) (John Hinz/Jennifer Rayner)
10:30	Review of Monocrotophos and Dicrotophos (Bob Benson/Bob Young)
12:00 p.m.	Lunch
1:00	Review of Methamidophos (Henry Anderson/Sylvia Talmage)
2:00	Review of Mevinphos (Daniel Sudakin/Jennifer Rayner)
3:00	Break
3:15	Review of Phosphamidon (Ed Bernas/Sylvia Talmage)
4:15	Review of Fenamiphos (George Woodall/Jennifer Rayner)
5:30	Adjourn for the day

Friday, September 11, 2009

8:30 a.m.	Review of Gasoline (John Hinz/Calvin Willhite/Sylvia Talmage)
9:30	Revisit of Hydrogen Selenide (Ernie Falke)
10:00	Review of Cadmium (Susan Ripple/Jennifer Rayner)
11:00	Review of Red Phosphorus (Glenn Leach/Bob Young)
12:00	Adjourn meeting

*See page 2.

ANY INFORMATION DISCUSSED AT THE NAC/AEGL MEETINGS IS CONSIDERED PUBLIC INFORMATION.

NAC/AEGL Meeting 49: September 9-11, 2009

ATTACHMENT 2

Please Return to Paul Tobin

Chemical: **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Bob Young
Cheryl Ba
Janice Payne
Sylvia Talon

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					John Hinz				
Marc Baril					Jim Holler				
Lynn Beasley					Clarion Johnson				
Alan Becker					Glenn Leach				
Robert Benson					Richard Niemeier				
Edward Bernas					Mattias Oberg				
Iris Camacho					Susan Ripple				
George Cushmac					George Rusch, Chair				
Richard Erickson					Daniel Sudakin				
Neeraja Erraguntla					Marcel vanRaaij				
David Freshwater					George Woodall				
Ralph Gingell					Alan Woolf				
Ernest V. Falke					Paul Tobin				
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** _____ **Second by:** _____
AEGL 2 **Motion by:** _____ **Second by:** _____
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** _____

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
LEAD
(CAS Reg. No. 7439-92-1)

NAC/AEGL-49
September 9-11, 2009

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: George Woodall

Chemical Reviewers:Lynn Beasley, Marcel van Raaij

Lead

Conversion
1 ppm= 8.5 mg/m^3

Physical Characteristics
- Solid-Bluish white, silver gray metal

Uses
- Consumer and industrial materials
- Lead-acid storage batteries
- Paint pigments, glass, plastics, ceramics

Metabolism and Disposition
- Not metabolized, forms complexes with proteins and non protein ligands
- Half-life in blood ~ 30 days, trabecular bone 100-700 days, cortical bone 10^4 days
- Distributed to soft tissues and excreted in urine and feces
- Stored in bones

Human Exposure

- Inhalation of lead containing particles, cigarette smoke, fumes/dust in occupational setting
- Grimsley and Adams-Mount (1994)- 0.525 mg/m^3 at worksite: persistent headache, nausea, dizziness, anorexia, joint pain after a few weeks of cutting painted (lead-based) steel beams
- Wang et al. (2002)- 0.206 mg/m^3 average airborne lead concentration at lead battery plant- blood lead levels lower in those drinking milk daily, higher in smokers, higher than 60 µg/dL and abnormal blood-urea nitrogen and uric acid values could be indicators of renal dysfunction
- Cullen et al. (1983)- 30 case reports of lead inhalation lasting 5 weeks-40 years. Abdominal pain, anemia with hemolysis, fatigue, and headache were associated with exposures lasting 6 months or less. Arthralgia, fatigue, abdominal pain, decreased libido, and increased serum uric acid were associated with exposures lasting longer than 6 months.
- Most data look at blood lead levels (PbB) and relate that to toxicity (ATSDR 2007)
  - <10 µg/dL PbB associated with adverse effects in adults
  - Thresholds for some sensitive effects in humans not identified
  - Children more sensitive to lead than adults- <5 µg/dL PbB

Predicting PbB

- Models used to predict PbB
  - O'Flaherty Model
    1. Simulates lead kinetics from birth through adulthood
    2. Relies on physiologically based parameters to determine lead disposition
    3. Short-term and long term exposures
  - Leggett Model
    1. Based on human and animal kinetics data
    2. Exposures at any age, acute (1 day) or chronic exposures
    3. Baseline adult PbB 2 µg/dL
    4. Does not have an exposure model-must simulate exposure scenario by calculating intakes and adding to the model
    5. Used for radiation risk assessment
  - Integrated Exposure Uptake Biokinetic Model
    1. PbB in children 0-7 years old exposed to environmental lead from many sources- risk of ≥10 µg/dL PbB
    2. Employs site-specific information and performs well comparing predicted and observed PbB, has been validated
    3. Contains compartment for air (0.1 µg/m^3 default) but automatically adds dietary contribution even when input is 0
    4. Cannot assess short-term, periodic, or acute exposures (at least 1 d/wk for 90 d)

Animal Exposure

Species	Concentration (mg/m^3)	Exposure Time	Effect	Reference
Rat	Lead Acetate 500 1000	6 hr/d, 5 d/wk for 4 wk	↓ body weight gain, ↑ relative spleen, liver, kidney weight, hepatic swelling and erythopoiesis, renal tubular degeneration, epithelial hyperplasia in terminal bronchioles. Type-II pneumocyte hyperplasia, focal fibrosis in the lung	Liao et al. 1995 (abstract only)
Rat	Lead Oxide 5	6 hr/d GD 2-3, 6-10, 13-17, 20	No effects	Coffigny et al. 1994

Next Steps

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR DICHLORVOS (CAS Reg. No. 62-73-7)

NAC/AEGL-49
September 9-11, 2009

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: John Hinz

Chemical Reviewers: Iris Camacho, Dieter Heinz

Dichlorvos

Common Synonyms: DDVP, Novatox, Vapona, 2,2-dichloroethenyl dimethylphosphate

Conversion
1 ppm= 9.17 mg/m^3
1 mg/m^3= 0.111 ppm

Physical Characteristics:
- Liquid-colorless to amber
- **Vapor Pressure = 1.2 x 10^{-2} mm Hg @ 20°C**

Uses:
- Internal and external organophosphate pesticide

Interspecies UF = 1

- Humans are no more sensitive or less sensitive than laboratory species (Cervoni et al., 1969; Pena-Chavarria et al., 1969; Hine and Slomka 1970; Snow and Watson 1973; Snow 1973; Twomey 2002a,b,c; MacGregor et al. 2005).

Intraspecies UF = 1
- An intraspecies uncertainty factor not required to account for polymorphisms of dichlorvos "A"-esterases in the human population or for differences in humans based on age, sex, or health status (Cavagna 1969; Cervoni et al. 1969; Pena-Chavarria et al. 1969; Cavagna 1970; Traverso et al., 1989).

AEGL-1 Values for Dichlorvos

10-minute	30-minute	1-hour	4-hour	8-hour
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

Key Study: Hunter, C.G. (1970a) Dichlorvos: inhalational exposures with human subjects. Part 1. Report No. TLGR.0061.70. Sittingbourne, Shell Research Ltd.
Menz, M., H. Luetkmeier, and K. Sachsse. 1974. Long-term exposure of factory workers. Arch. Environ. Health. 28:72-76.

Toxicity endpoint: No clinical signs of organophosphate poisoning or signs of irritation in volunteers exposed for 3-7.7 hr to an average concentration of 1 mg/m^3; supported by no clinical signs of organophosphate poisoning or signs of irritation in workers exposed for 8 months to ~0.7 mg/m^3.

Time scaling: None

Uncertainty factors: A total uncertainty factor of 1 was applied to
Interspecies: 1; Human data were used.
Intraspecies: 1; Documented lack of variability in sensitivity among different age groups and genders, and no known genetic polymorphisms in DDVP-ase in the population.

The AEGL level was held constant across all exposure time points. This approach is considered appropriate because humans exposed during working hours for 8 months to dichlorvos experienced no changes in effects during the exposure and 4 month follow-up period.

AEGL-2 Values for Dichlorvos

10-minute	30-minute	1-hour	4-hour	8-hour
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

Key Study: Atis, S., U. Comelekoglu, B. Coskun, A. Ozge, Ersoz, and D. Talas. 2002. Electrophyisological and histopathological evaluation of respiratory tract, diaphragm, and phrenic nerve after dichlorvos inhalation in rats. Inhal. Toxicol. 14: 199-215.
Blair, D., K.M. Dix, P.F. Hunt, E. Thorpe, D.E. Stevenson, and A.I. T. Walker. 1976. Dichlorvos – a 2-year inhalation carcinogenicity study in rats. Arch. Toxicol. 35:281-294.

Toxicity endpoint: Highest experimental exposure (5 mg/m^3) without an AEGL-2 tier effect.

Time scaling: None

Uncertainty factors: A total uncertainty factor of 1 was applied to Interspecies: 1; No mechanistic differences in dichlorvos poisoning in animals and humans. Humans are no more sensitive and possibly less sensitive than laboratory species to dichlorvos. Intraspecies: 1; Documented lack of variability in sensitivity among different age groups and genders, and no known genetic polymorphisms in DDVP-ase in the population.

The AEGL level was held constant across all exposure time points. This approach is considered appropriate because rats exposed for 2 years to 5 mg/m^3 dichlorvos for 23 hr/d experienced no changes in effects during the exposure period.

AEGL-3 Values for Dichlorvos

10-minute	30-minute	1-hour	4-hour	8-hour
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

Key Study: Dean B.J. and E. Thorpe. 1972a. Cytogenetic studies with dichlorvos in mice and Chinese hamsters. Arch. Toxikol. 30:39-49.

Toxicity endpoint: Highest experimental exposure and longest duration (72 mg/m^3 for 16 hr) without mortality. Supported by MacDonald (1982)- ~LC_{50}/3 = 66 mg/m^3

Time scaling: None

Uncertainty factors: A total uncertainty factor of 1 was applied to Interspecies: 1; No mechanistic differences in dichlorvos poisoning in animals and humans. Humans are no more sensitive and possibly less sensitive than laboratory species to dichlorvos.
Intraspecies: 1; Documented lack of variability in sensitivity among different age groups and genders, and no known genetic polymorphisms in DDVP-ase in the population.

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 subchronic human and chronic animal studies.

New Data-

MacDonald 1982
Male and female Wistar Rats (5/sex/group); 4 hour head-only exposure

4 hr-LC_{50} > 198 mg/m^3 based on mortality in the highest exposure groups; 13 of 40 died following exposure to 198-250 mg/m^3. Total mortality for the study was 14 of 60 or 23%.

Concentration	Effect
85 mg/m^3 (9.4 ppm)	10% mortality; lethargy, hypersensitivity to noise; subdued
142 mg/m^3 (15.8 ppm)	Lethargy, hypersensitivity to noise; subdued; body tremors
198 mg/m^3 (22 ppm)	Lethargy, hypersensitivity to noise; body tremors
206 mg/m^3 (22.9 ppm)	Lethargy, hypersensitivity to noise; subdued; body tremors; ataxia
210 mg/m^3 (23.3 ppm)	100% mortality; hypersensitivity to noise; splayed gait, hypothermia; hind leg paresis; pulmonary congestion
250 mg/m^3 (27.8 ppm) (oversaturated)	30% mortality; lethargy, hypersensitivity to noise; subdued; ataxia

AEGL-3
Remain the same- Highest nonlethal experimental concentration 72 mg/m^3, 8.0 ppm
198 mg/m^3 = less than 4-hr LC_{50}, 66 mg/m^3, 7.3 ppm
206 mg/m^3 = Discount 85 mg/m^3, highest nonlethal experimental concentration, 206 mg/m^3, 22.9 ppm

Summary of AEGL Values for Dichlorvos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	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
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
AEGL-3 (Lethal)					

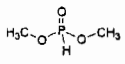
Summary of AEGL Values for Dichlorvos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	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
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
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

ATTACHMENT 5

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

Dimethyl Phosphite



NAC/AEGL-49
September 9-11, 2009
Research Triangle Park, NC

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Cushmac

Chemical Reviewers: David Freshwater and George Rusch

Limited human and animal data sets

Structurally similar to organophosphate insecticides that inhibit cholinesterase activity

However, DMP does not appear to be a cholinesterase inhibitor.

Repeated-exposure inhalation studies in rats did not indicate systemic or cumulative toxic effects suggesting cholinesterase inhibition.

Instead, clinical signs from both acute and repeated-exposure animal studies suggest that DMP is an irritant

Effects included lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion.

AEGL-1 Values for Dimethyl Phosphite				
10-min	30-min	1-h	4-h	8-h
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

AEGL-2 values for Dimethyl Phosphite				
10-minute	30-minute	1-hour	4-hour	8-hour
120 ppm	120 ppm	95 ppm	60 ppm	39 ppm

Species: Mouse
Concentration: 1575 ppm
Time: 6 hours
Endpoint: Clinical signs: labored breathing & ptosis
Reference: Hazleton, 1962

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. 30-min value adopted as 10-min value.

Uncertainty Factors:
Intraspecies: 3
Interspecies: 3

Considered sufficient because DMP is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Interspecies UF is also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours

Modifying Factor: 3: Sparse database, POD is nominal concentration.

Values considered protective: Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days.

Extrapolating across time using n=1 or n=3, and applying a total uncertainty factor of 10 (no MF is applied because this is a repeated-exposure study using analytical concentrations), yields values of 190 ppm for 10- and 30-min, 150 ppm for 1-hr, 96 ppm for 4-hr, and 63 ppm for 8-hr.

AEGL-3 values for Dimethyl Phosphite				
10-minute	30-minute	1-hour	4-hour	8-hour
360 ppm	360 ppm	290 ppm	180 ppm	120 ppm

Species: Mouse
Concentration: 1575 ppm
Time: 6 hours
Endpoint: Clinical signs: labored breathing & ptosis
Reference: Hazleton, 1962

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. 30-min value adopted as 10-min value.

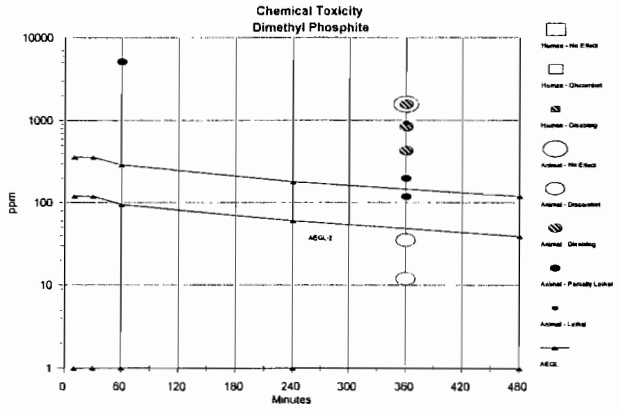
Uncertainty Factors:
Intraspecies: 3
Interspecies: 3

Considered sufficient because DMP is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Interspecies UF is also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours

Modifying Factor: None: Effects noted at POD are below definition of AEGL-3.

Values considered protective: Dividing the 1-hr rat LC_{50} of >5112 ppm (Albright and Wilson Inc., 1985) by 3, yields an estimated 1-hr lethality threshold of >1701 ppm. Applying a total uncertainty factor of 10, yields a value of >170 ppm; this concentration consistent with the derived 1-hr AEGL-3 value.



Note: Animal partially lethal data points at 360 minutes are from repeated exposure studies. Lethality was not noted until after 14-27 days of exposure.

Summary of AEGL values for Dimethyl Phosphite					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	120 ppm	120 ppm	95 ppm	60 ppm	39 ppm
AEGL-3 (Lethal)	360 ppm	360 ppm	290 ppm	180 ppm	120 ppm

No other standards or guidelines were located for dimethyl phosphite.

Another option for derivation of AEGL-3

Species: Rat
Concentration: 843 ppm
Time: 6 hr/day for 5 days
Endpoint: No mortality (one rat killed in extremis on day 1 at 943 ppm, next highest concentration tested)
Reference: Biodynamics, 1980a

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. 30-min value adopted as 10-min value.

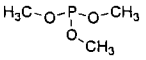
Uncertainty Factors:
Intraspecies: 3
Interspecies: 3

Summary of AEGL values for Dimethyl Phosphite					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	120 ppm	120 ppm	95 ppm	60 ppm	39 ppm
AEGL-3 (Lethal)	360 ppm 193 ppm	360 ppm 193 ppm	290 ppm 154 ppm	180 ppm 96 ppm	120 ppm 63 ppm

ATTACHMENT 6

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

Trimethyl Phosphite



NAC/AEGL-49
September 9-11, 2009
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ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Cushmac

Chemical Reviewers: David Freshwater and George Rusch

Limited human and animal data sets

Structurally similar to organophosphate insecticides that inhibit cholinesterase activity

However, TMP does not appear to be a cholinesterase inhibitor.

A study of cholinesterase inhibition following intravenous administration of TMP in rats, rabbits, and dogs and *in vitro* studies of cholinesterase inhibition potential showed that TMP does not inhibit cholinesterase activity.

Repeated-exposure inhalation studies in rats did not indicate systemic or cumulative toxic effects suggesting cholinesterase inhibition.

Instead, clinical signs from acute and repeated-exposure animal studies suggest that TMP is an irritant.

Effects included lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion.

AEGL-1 Values for Trimethyl Phosphite				
10-min	30-min	1-h	4-h	8-h
11 ppm	7.6 ppm	6.1 ppm	3.8 ppm	2.5 ppm

Species: Rat
Concentration: 10 ppm
Time: 6 hr/day, 5 days/week, 4 weeks
Endpoint: NOEL for clinical signs
Reference: Biodynamics, 1979

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. Time scaling was used to derive the 10-min value because the key study is repeated-exposure.

Uncertainty Factors:
Intraspecies: 3

Considered sufficient because TMP is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Interspecies: 1

An interspecies UF of 3 might normally be applied because TMP is an irritant. Use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human occupational exposure data (AEGL-1 values derived with a total UF of 10 are 3.3, 2.3, 1.8, 1.1, and 0.60 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm.

AEGL-2 values for Trimethyl Phosphite				
10-minute	30-minute	1-hour	4-hour	8-hour
110 ppm	77 ppm	61 ppm	38 ppm	25 ppm

Species: Rat
Concentration: 101 ppm
Time: 6 hr/day, 5 days/week, 4 weeks
Endpoint: Corneal opacities
Reference: Biodynamics, 1979

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points. Time scaling was used to derive the 10-min value because the key study is repeated-exposure.

Uncertainty Factors:
Intraspecies: 3

Considered sufficient because TMP is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Interspecies: 1

An interspecies UF of 3 might normally be applied because TMP is an irritant. Use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm.

AEGL-3 values for Trimethyl Phosphite				
10-minute	30-minute	1-hour	4-hour	8-hour
560 ppm	390 ppm	310 ppm	160 ppm	81 ppm

Species: Mouse
Concentration: 2150 ppm
Time: 3 hours
Endpoint: Estimated threshold for lethality (⅓ concentration causing up to 50% lethality)
Reference: Hazleton, 1962

Time Scaling:
$C^n \times t = k$, where n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points.

Uncertainty Factors:
Intraspecies: 3
Interspecies: 3

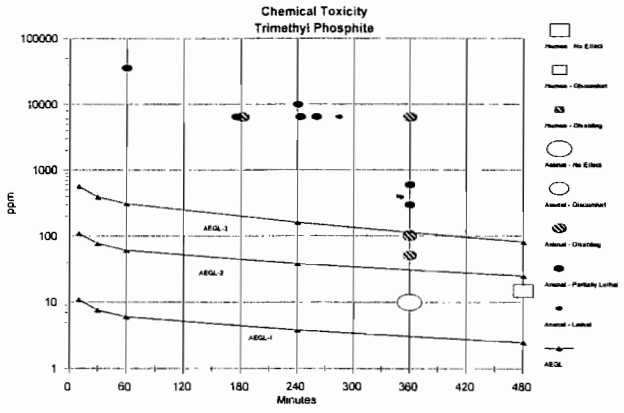
Considered sufficient because TMP is an irritant and clinical signs are likely caused by a direct chemical effect on the tissues. This type of portal-of-entry effect is not likely to vary greatly between species or among individuals.

Values considered protective:

Dividing the 4-hr rat LC_{50} of >10,000 ppm (Levin and Gabriel, 1973) by three yields an estimated 4-hr lethality threshold of 3000 ppm; applying a total uncertainty factor of 10, yields a 4-hr AEGL-3 value of 300 ppm.

No deaths were noted in rats exposed to approximately 100 ppm TMP 6 hr/day, 5 days/week for 4 weeks (Biodymanics, 1978, 1979; Mobil Oil, 1979).

Extant standards and guidelines for trimethyl phosphate					
Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	11 ppm	7.6 ppm	6.1 ppm	3.8 ppm	2.5 ppm
AEGL-2	110 ppm	77 ppm	61 ppm	38 ppm	25 ppm
AEGL-3	560 ppm	390 ppm	310 ppm	160 ppm	81 ppm
TLV-TWA (ACGIH)					2 ppm
MAC-Peak Category (The Netherlands)					2 ppm



NAC 44, December 2007
NAC-46, December 2008

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL IODIDE (CH_3I)

National Advisory Committee for AEGLs Meeting 49
Research Triangle Park, NC
September 9-11, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Alan Becker

Chemical Reviewers:
Ed Bernas
John Hinz

METHYL IODIDE

Used as a biocide prior to planting of crops such as strawberries and tomatoes
Liquid injected into soil rapidly vaporizes
Sweet, ethereal odor

Human Studies:
- Clinical and case studies provide insufficient data to derive AEGL values
  - Clinical studies available for the related chemical, methyl chloride

Animal Studies:
- Acute toxicity, including neurotoxicity; repeat-dose, developmental/reproductive toxicity; genotoxicity; and chronic toxicity/carcinogenicity
- Recent well-conducted toxicity studies available only from secondary source – (U.S. EPA 2006) and discussed in 2009 issue of Inhalation Toxicology

Metabolism

Monohalomethanes are conjugated with the tripeptide glutathione.
- Glutathione is a detoxifying agent
- Protects cells from oxidizing agents which might otherwise damage them.
- Oxidizing agents react with the –SH group of cysteine of glutathione instead of doing damage elsewhere....

Conjugation may be either enzymatic, via glutathione transferase, or non-enzymatic.
Glutathione transferase activity is higher in rodent tissues than in human tissues
- **Mouse and rabbit more sensitive than rats to glutathione depletion

For other monohalomethanes, enzymatic conjugation with glutathione is thought to vary no more than 3-fold in humans (Nolan et al. 1984).

Modes of Action

Lesions of the nasal passages, specifically the olfactory epithelium
- Due to glutathione depletion in nasal tissue

Neurotoxicity
- Due to modification of ion currents in nerve cells (glutathione depletion?)

METHYL IODIDE

Uncertainty factors

Uncertainty factors:
Interspecies: 1
Greater chemical uptake in rodents based on blood:air partition coefficients
- rat: 39; human 18 (Sweeney et al. 2009), and
- higher respiratory rate and cardiac output in rodents

When inhaling similar concentrations of the related chemical methyl chloride, blood concentrations are higher in rats than in humans.
- methyl chloride: human uptake one-half of that of rat at steady-state (50 ppm)

Tissue levels of glutathione transferase are higher in rodents than in humans.
Rodents and rabbits are more sensitive than humans to glutathione depletion.
Sensitive species:
- The rabbit fetus does not regulate the uptake of iodide.

Intraspecies: 3
Metabolism via glutathione conjugation is not expected to vary greatly among humans (Nolan et al. 1985). Furthermore, conjugation with glutathione may be non-enzymatic, which could further minimize individual differences.

Time-scaling:

The glutathione depletion which may be responsible for olfactory epithelial lesions and neurotoxicity is considered on a continuum with lethality. Therefore, all AEGL levels were time-scaled. The time-scaling value of n of 2.0 was calculated by entering four sets of acute toxicity data for rats into the Log Probit Model program. The threshold for lethality was set at the lower limit of the 95% confidence limit for each exposure duration.

AEGL-1: Animal Data (Rat) – Weight-of-evidence approach

27 ppm for 6 hours: NOAEL for neurotoxicity (U.S. EPA 2006)
100 ppm for 1 hour: no observable change, nasal passages (Reed et al. 1995)
100 ppm for 6 hours: no effect on respiratory parameters (DeLorme et al. 2009)
25 ppm for 6 hours/day, 5 days/week, 4 weeks: NOAEL for nasal lesions and neurotoxicity (Monsanto et al. 1983)
21 ppm for 6 hours/day, 5 days/week for 13 weeks: NOAEL for nasal lesions and other effects (U.S. EPA 2006)

Point of departure: 27 ppm for 6 hours
Uncertainty factors of 1and 3
To time-scale or not to time-scale? Values were time-scaled ($C^{2.0} \times t = k$)
Because POD was neurotoxicity and not irritation
Time-scaled to 10 minutes - the value of n was based on 1-, 4-, and 6-hour studies.
8-hour value set equal to the 4-hour value based on subchronic NOAEL

Proposed AEGL-1 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
54 ppm	31 ppm	22 ppm	11 ppm	11 ppm

AEGL-2
Key Study – Rat (Reed et al. 1995)

100 ppm for 0.5 hours: no observable change, nasal passages
100 ppm for 1 hour: no observable change, nasal passages
100 ppm for 2 hours: minimal lesions, olfactory epithelium
100 ppm for 3 hours: slight lesions, olfactory epithelium
100 ppm for 4 hours: moderate lesions, olfactory epithelium
100 ppm for 6 hours: reversible lesions of the olfactory epithelium

Point of departure was 100 ppm for 6 hours
Uncertainty factors of 1 and 3
Values were time-scaled ($C^{2.0} \times t = k$)
Time-scaled to 10 minutes - the value of n was based on 1-, 4-, and 6-hour studies.

Proposed AEGL-2 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
200 ppm	120 ppm	82 ppm	41 ppm	29 ppm

AEGL-3

Key Studies with the Rat
1-Hour study (Eastman Kodak Co. 1987)
Mortalities of 20%, 60%, 90% at 1190 ppm, 1554 ppm, 1973 ppm, respectively
4-Hour study (U.S. EPA 2006)
Mortalities of 0%, 80%, 80%, 100% at 581 ppm, 710 ppm, 797 ppm, and 1198 ppm
6-hour study (U.S. EPA 2006)
Mortalities of 0%, 0%, and 4% at 27, 93, and 401 ppm
0.5 -6-hour study at 100 ppm (Reed et al. 1995)
No mortalities

All data sets entered into Log Probit Model program:
Values set at the lower limit of the 5% response for lethality (the lower limit of the 95% confidence limit). This value is similar to the benchmark dose, $BMCL_{05}$.
Values automatically time-scaled; time scaling value (n) = 2.0
Uncertainty factors of 1 and 3

Proposed AEGL-3 Values for Methyl Iodide				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
670 ppm	400 ppm	290 ppm	150 ppm	98 ppm

METHYL IODIDE

Proposed Methyl Iodide AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	54 ppm	31 ppm	22 ppm	11 ppm	11 ppm
AEGL-2	200 ppm	120 ppm	82 ppm	41 ppm	29 ppm
AEGL-3	670 ppm	400 ppm	290 ppm	150 ppm	98 ppm

AEGL-1: based on weight of evidence approach. The point of departure was a NOAEL for clinical signs in the rat, 27 ppm for 6 hours. Interspecies and intraspecies uncertainty factors of 1 and 3, respectively, were applied.
AEGL-2: based on reversible lesions of the olfactory epithelium, 100 ppm for 6 hours. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied.
AEGL-3: based on 1-, 4-, and 6-hour $BMCL_{05}$ values calculated with the Log Probit Model program. Inter- and intraspecies uncertainty factors of 1 and 3, respectively, were applied
Time-scaling: $C^2 \times t = k$

METHYL IODIDE

Comparison of AEGL values for monohalomethanes:

AEGL Values for Halomethanes					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
Methyl Iodide					
AEGL-1	54 ppm	31 ppm	22 ppm	11 ppm	11 ppm
AEGL-2	200 ppm	120 ppm	82 ppm	41 ppm	29 ppm
AEGL-3	670 ppm	390 ppm	280 ppm	130 ppm	86 ppm
Methyl Bromide					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm
AEGL-3	3300 ppm	1300 ppm	740 ppm	230 ppm	130 ppm
Methyl Chloride					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1100 ppm	1100 ppm	910 ppm	570 ppm	380 ppm
AEGL-3	3800 ppm	3800 ppm	3000 ppm	1900 ppm	1300 ppm

NR = Not Recommended; values are not recommended because there are no odor or warning properties and toxic effects may occur below the odor threshold.

AEGL values reflect the known toxicity: MeI>MeBr>MeCl.

METHYL IODIDE

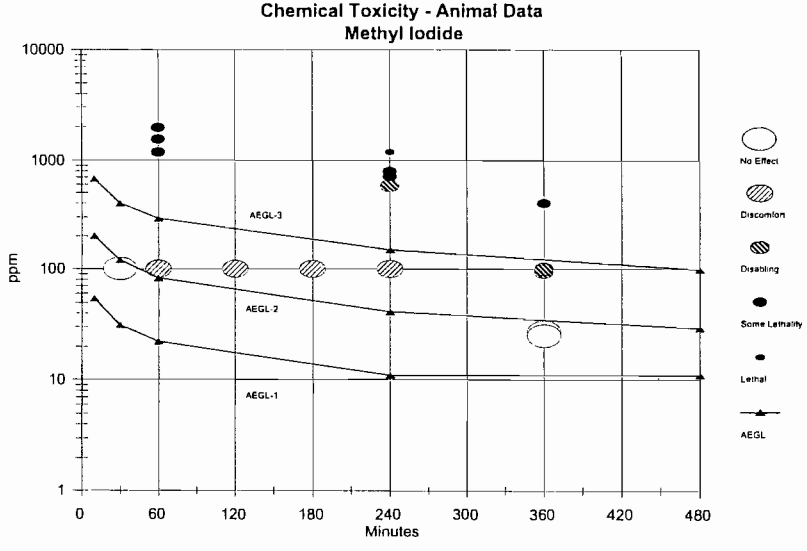
Comparison of LC_{50} values for monohalomethanes – rat data

Chemical	1-h LC_{50}	4-h LC_{50}	Uncertainty Factors	Reference
MeI	1458 ppm	691 ppm	1,3	Eastman-Kodak 1987; U.S. EPA 2006
MeBr	1880 ppm	780 ppm	1,3	Zwart et al. 1992 ; Kato et al. 1986
MeCl	6-h repeat exposure to 5000 ppm - no mortality		1,3	Morgan et al. 1982; Chellman et al. 1986

Species with high levels of glutathione-S-transferase (mouse) appear to be more sensitive to the toxicity of monohalomethanes.

The values derived for MeCl are supported by clinical studies (200 ppm for 3-3.5 hours = no effect; repeat exposure to 150 ppm for 7.5 hours = no effect).

METHYL IODIDE



ATTACHMENT 8

PHOSGENE: REVISION OF FINAL VALUES CONSIDERING NEW DATA

NAC/AEGL-49
September 9-11, 2009
RESEARCH TRIANGLE PARK, NC

Cheryl Bast

Ernie Falke

Bill Bress
David Belluck
Larry Gephart

Current Phosgene AEGL Values

Published in Volume 2

Little species variability

Steep concentration-response

Time scaling: n = 1

UF: 3 x 3 = 10

AEGL-2:

Key Study: Gross, P., W.E. Rinehart and T. Hatch. 1965. Chronic pneumonitis caused by phosgene: an experimental study. Arch Environmental Health 10:768-775.

POD: Chemical pneumonia in rats (2 ppm; 1.5 hr); Chronic pneumonitis noted at lower cencentrations/durations

AEGL-3:

Key Study: Zwart, A., J.H.E. Arts and J.M. Klokman-Houweling. 1990. Determination of concentration-time-mortality relationships to replace LC_{50} values. Inhalation Toxicology 2:105-117.

Whole body study. Exposure atmospheres well-circulated in chamber.

POD: Highest concentration causing no death in rats after a 10-min (36 ppm) or 30-min (15 ppm) exposure.

Phosgene AEGL Values: Recent data considerations

Steep concentration-response

Time scaling: n = 1

UF: 3 x 1 = 3

Rat lethality study: Pauluhn, J. 2006a. Acute nose-only exposure of rats to phosgene. Part I. Concentration x time dependence of LC_{50}s, non-lethal-threshold concentrations and analysis of breathing patterns. Inhalation Toxicology 18:423-435.

Rat lung parameter study: Pauluhn, J. 2006b. Acute nose-only exposure of rats to phosgene. Part II. Concentration x time dependence of changes in bronchoalveolar lavage during a follow-up period of 3 months. Inhalation Toxicology 18:595-607.

Dog study: Pauluhn, J. 2006c. Acute head-only exposure of dogs to phosgene. Part III. Comparison of indicators of lung injury in dogs and rats. Inhalation Toxicology 18:609-621.

Dogs sacrificed 24-hr post-exposure

Pauluhn Data Conclusions:

- Dog is better model to extrapolate to humans (physiology of respiratory tract and acinar structure of the lung)

- For AEGL value derivation from rodent data, it is more appropriate to utilize rodent studies of at least 30-minutes so that a stable breathing pattern has been achieved.

  The validity of Haber's Law is complicated by the fact that high concentrations of phosgene stimulate protective reflexes in rodents; whereas, similar changes do not occur in humans and larger animals (dog).

  Thus, it may be difficult to extrapolate to humans from high phosgene exposure concentrations of short duration in rodents.

  Rats exhibited a transient decrease in respiration during the first 10-15 minutes of exposure, leading to a decreased inhaled concentration of phosgene.

  Thus, the c x t products noted at short duration and high concentration may be higher than those obtained at longer exposure durations, suggesting an apparent lower toxicity at the short-duration x high-concentration exposures.

- Pauluhn studies suggest that phosgene is slightly more toxic than found in older studies: Likely due to increased purity of phosgene

- Intraspecies UF of 3 and Interspecies UF of 1 justified

Intraspecies UF: 3

•Steep concentration-response curve implies limited intra-individual variability.

Duration	Concentration	Mortality (Rats)
10 min.	52.3 ppm	2/10
	61.9 ppm	6/10
30 min.	13.4 ppm	4/10
	16.7 ppm	10/10
1 hr.	7.4 ppm	4/10
	11.8 ppm	10/10

•Mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals.

Interspecies UF: 1

Lethal and non-lethal toxicity data in multiple species suggest that smaller animals may be more susceptible to inhaled phosgene than larger animals.

LETHAL

The LCT_{50} values are essentially constant for monkeys, guinea pigs, mice, and rats, with values ranging from approximately 400 to 600 ppm·min.

Larger species appear to be between four to eight-fold less sensitive than rodents with regard to lethality.

These conclusions are complicated by the fact that only data from rat and mouse studies were consistently of high quality.

NON-LETHAL

In rats, c x t products of between 48 ppm·min and 60 ppm·min induced increased protein in BAL fluid, and no increase was noted from 24-30 ppm·min.

In mice and hamsters, a c x t product of 48 ppm·min induced an increase of protein in BAL fluid, and no increase was noted at 24 ppm·min.

In dogs, a c x t product of 129 ppm·min was necessary to cause an increase in protein in BAL fluid, and no increase was observed at 63 ppm·min.

The CT product required to induce an increase in protein in BAL fluid in dogs is approximately two-fold greater than in rodents, and the NOAEL for increased BAL protein in dogs (63 ppm·min) is higher than the LOAEL values in rodents (48-60 ppm·min).

With regard physiology of the respiratory tract and acinar structure of the lung, dogs are more similar to humans than rodents.

Collectively, these data suggest that an interspecies uncertainty factor of no more than 1 is justified when extrapolating from rodents to humans

Mean LCT_{50} Values And BAL Protein for Various Species					
Species	LCT_{50} (ppm· min)	LCT Study Quality	BAL Protein CT NOAEL (ppm· min)	BAL Protein CT LOAEL (ppm· min)	BAL Study Quality (Reference)
Monkey	370	Poor. No experimental details described.	-	-	-
Guinea pig	488		-	-	-
Mouse	550	GLP Study (Zwart et al., 1990)	24 (0.1 x 240)	48 (0.2 x 240)	Well-conducted study, analytical methods (Hatch et al., 1986)
Rat	615	GLP Studies (Pauluhn, 2006a; Zwart et al., 1990)	24 (0.1 x 240) 30 (1 x 30)	48 (0.2 x 240) 60 (2 x 30)	GLP Study (Pauluhn, 2006b)
Hamster	-	-	24 (0.1 x 240)	48 (0.2 x 240)	Well-conducted study, analytical methods (Hatch et al., 1986)
Rabbit	1500	Poor. No experimental details descried.	-	-	-
Dog	2100		63 (2.1 x 30)	129 (4.3 x 30)	GLP Study (Pauluhn, 2006c)
Goat	2600		-	-	-
Sheep	3300		-	-	-

AEGL-1 Values for Phosgene				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
NR	**NR**	**NR**	**NR**	**NR**

NR: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

No change from published values.

AEGL-2 values for Phosgene				
10-minute	30-minute	1-hour	4-hour	8-hour
2.0 ppm	0.67 ppm	0.33 ppm	0.067 ppm	0.033 ppm

Species: Rat
Concentration/Time: 2 ppm/ 30 min (10-min, 30-min, 1-hr)
0.2 ppm/4 hr (4-hr, 8-hr)
Endpoint: Increased protein in BAL fluid
Reference: Pauluhn, 2006b

Time Scaling:

$C^n \times t = k$, where n= 1

Uncertainty Factors:
Intraspecies: 3
Interspecies: 1

Values considered protective: No significant treatment-related effects were noted in rats exposed to 0.125 ppm phosgene 4 hours/day, 5 days/week for 17 weeks (Franch and Hatch, 1986).

AEGL-3 values for Phosgene				
10-minute	30-minute	1-hour	4-hour	8-hour
5.0 ppm	1.7 ppm	1.3 ppm	0.33 ppm	0.16 ppm

Species: **Rat**
Concentration/Time: **5.0 ppm/ 30 min (10-min, 30-min)**
3.9 ppm/ 1 hr (1 hr, 4-hr, 8-hr)
Endpoint: **$BMCL_{05}$**
Reference: **Pauluhn, 2006a**

The 10-minute $BCML_{05}$ value is not used to derive the 10-minute AEGL-3 value because rats exhibit a transient decrease in respiration during the first 10-15 minutes of exposure, leading to a decreased inhaled concentration of phosgene.

Time Scaling:

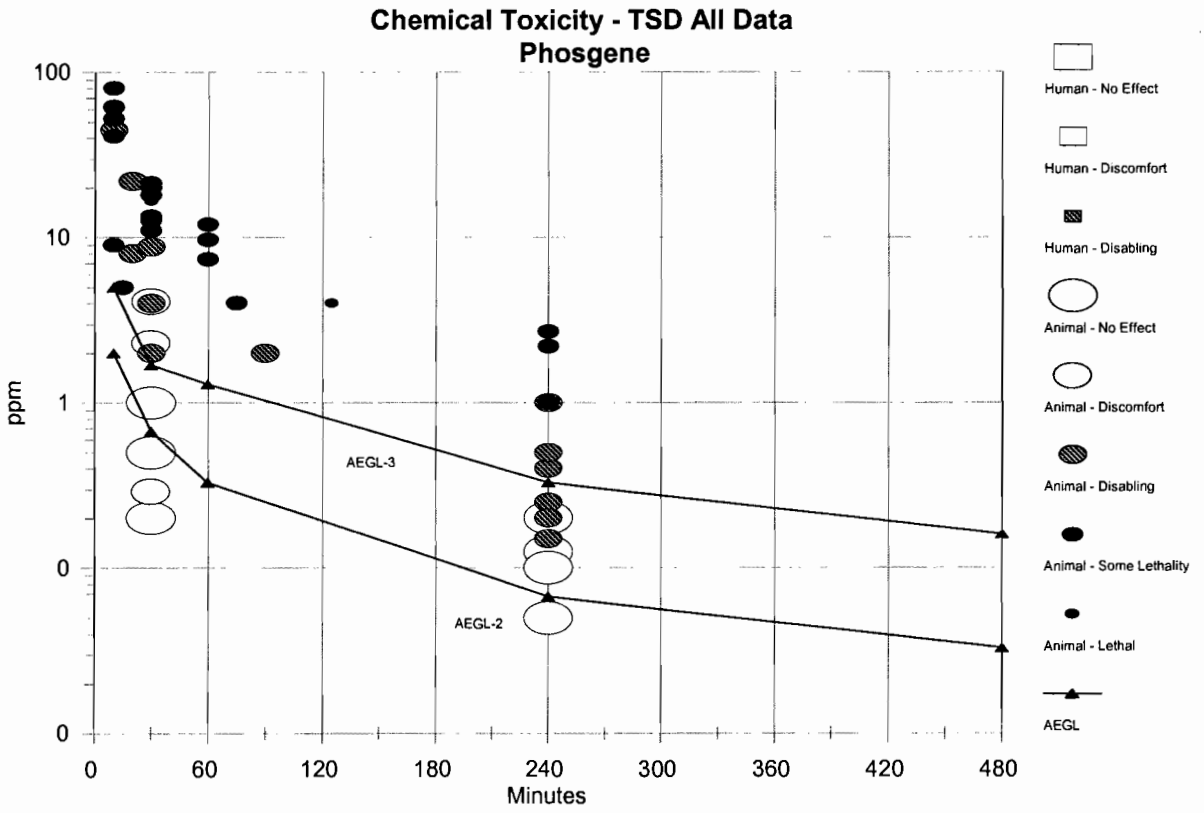
$C^n \times t = k$, where n= 1

Uncertainty Factors:
Intraspecies: 3
Interspecies: 1

Values considered protective: No deaths were noted in approximately 200 workers exposed to phosgene concentrations ranging from 50 to 300 ppm·min (Kaerkes, 1992), and calculated AEGL-3 values range from 50 to 79 ppm·min.

No deaths were noted in rats exposed to phosgene 6 hrs/day at concentrations of 0.1 ppm (5 days/week), 0.2 ppm (5 days/week), 0.5 ppm (2 days/week) or 1.0 ppm (1 day/week) for 4 or 12 weeks (Kodavanti et al.,1997).

Extant Standards and Guidelines for Phosgene					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.0 ppm	0.67 ppm	0.33 ppm	0.067 ppm	0.033 ppm
AEGL-3	5.0 ppm	1.7 ppm	1.3 ppm	0.33 ppm	0.16 ppm
ERPG-1[a]			NA		
ERPG-2[a]	0.5 ppm				
ERPG-3[a]	1.5 ppm				
EEGL (NRC)[b]			0.2 ppm		0.02 ppm (24-hr)
NIOSH IDLH[c]	2 ppm				
NIOSH STEL[d]	0.2 ppm (15-min ceiling)				
NIOSH REL[d]					0.1 ppm (10-hr)
OSHA PEL-TWA[e]					0.1 ppm
ACGIH TLV[f]					0.1 ppm
MAK (Germany)[g]					0.1 ppm
MAC (Netherlands)[h]					0.02 ppm


Chemical Toxicity - TSD All Data
Phosgene
100
10
1
0
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

Comparison of Published (Volume 2) Phosgene AEGL values with Values derived from new rat data.

Summary of AEGL Values for Phosgene [ppm]						
Classification	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR *NR*	NR *NR*	NR *NR*	NR *NR*	NR *NR*	-
AEGL-2	0.60	0.60	0.30	0.08	0.04	POD: 2 ppm, 1.5 hours. Chemical pneumonia rats Reference: Gross et al., 1965 n=1 UF = 3 x 3
	2.0	*0.67*	*0.33*	*0.067*	*0.033*	*10-min, 30-min, & 1-hr POD: 2 ppm, 30 min.* *4-hr & 8-hr POD: 0.2 ppm, 4 hr.* *LOAEL for increased protein in BAL fluid in rats, resolved by Day 7 post-exposure.* *Reference: Pauluhn, 2006b* *n = 1* *UF = 3 x 1*
AEGL-3	3.6	1.5	0.75	0.20	0.09	10-min POD: 36 ppm, 10-min 30-min, 1-hr, 4-hr, & 8-hr POD: 15 ppm, 30-min. Highest concentration causing no mortality in the rat after a 10-, or 30-min exposure Reference: Zwart et al., 1990 n=1 UF = 3 x 3
	5.0	*1.7*	*1.3*	*0.33*	*0.16*	*10-min, 30-min POD: 5.0 ppm, 30-min; 30-min rat $BMCL_{05}$* *1-hr, 4-hr, & 8-hr POD: 3.9 ppm, 1-hr;.1-hr rat $BMCL_{05}$* *Reference: Pauluhn, 2006b* *n = 1* *UF = 3 x 1*

Dr. Pauluhn's Comments on Revised TSD:

"The modified derivation is very well justified.

However, taking into account the spirit of the discussion we have had in April, I am not entirely sure whether the lowering of AEGL-2 for 4-hr and 8-hr values meets the deliberations of the expert group.

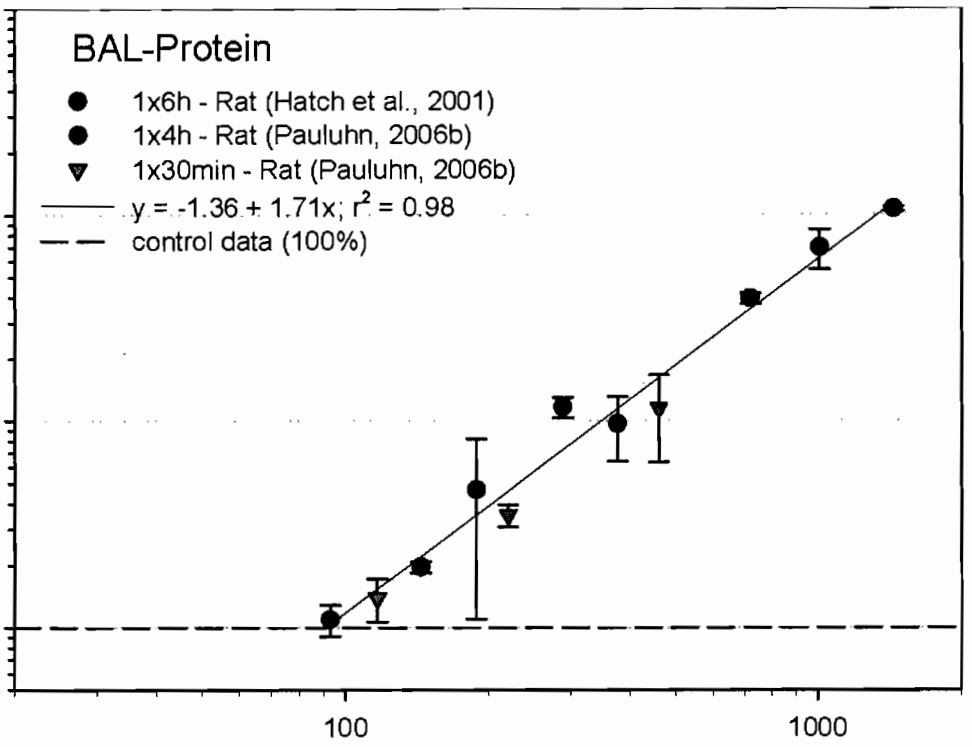
I attached some thoughts which may overcome this potential challenge:

- The AEGL-2 derivation utilizes two different time-dependent values for increased protein in BAL. Please be so kind to consider a slightly modified approach which could be justified as follows:

  Taking into account the BAL-protein from 30-min, 4-hr, and 6-hr (Hatch), the maximum non-lethal elevation of BAL-protein at the LCt01 level is 100-times the control level (the control is defined as 100%; thus, 5% becomes 500%; BAL data were compared to the time-matched concurrent control). If one would take this as starting point to calculate the BMCxt at 5% level then the equation shown in the figure becomes log(500) = -1.36 + 1.71x [x = empirical Cxt in mg/m^3 x min].

  Interestingly, this then gives a statistically derived BMC05 of 59 ppm x min, in other words, exactly that value which has been derived using the current approach for shorter exposure durations. However, this alternative approach would allow using the same factor for all time points as it considers empirical Cxt's covering almost the entire range."

SUGGESTION: Use 30-min POD and time scale.



Concentration X Time (mg/m^3 x min)

LCt01 = 100-times the control level of BAL-protein. When using the BMCxt5-time the control then BMCx5% equivalent would be 59 ppm x min.

- While reading through the text, I thought that the justifications given for the uncertainty factor for AEGL-3 implicit that the only variability left is 'inhaled dose'. Then children become the critical subpopulation left. Commonly, the infant to adult human minute ventilation is adjusted by an UF of 2. In the light of the in depth of explanations given for the UFs used for both AEGL-2 and AEGL-3, a 'dosimetric UF' of 2 appears to be also defensible.

SUGGESTION: Retain UF of 3; Most consistent with SOP.

Extant Standards and Guidelines for Phosgene					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.0 ppm	0.67 ppm	0.33 ppm	~~0.067 ppm~~ 0.083 ppm*	~~0.033 ppm~~ 0.042 ppm*
AEGL-3	5.0 ppm	1.7 ppm	1.3 ppm	0.33 ppm	0.16 ppm
ERPG-1[a]			NA		
ERPG-2[a]	0.5 ppm				
ERPG-3[a]	1.5 ppm				
EEGL (NRC)[b]			0.2 ppm		0.02 ppm (24-hr)
NIOSH IDLH[c]	2 ppm				
NIOSH STEL[d]	0.2 ppm (15-min ceiling)				
NIOSH REL[d]					0.1 ppm (10-hr)
OSHA PEL-TWA[e]					0.1 ppm
ACGIH TLV[f]					0.1 ppm
MAK (Germany)[g]					0.1 ppm
MAC (Netherlands)[h]					0.02 ppm

*30-min POD

***Pauluhn (2006a)* vs. Zwart et al. (1990) rat lethality data**			
Duration	Concentration (ppm)	Mortality	LC (ppm)
10-minutes			
	12	0/10	LC_{50} = 82 ppm *LC_{50} = 62 ppm*
	*36	0/10	
	41.1	*3/10*	
	44.8	*0/10*	$BMCL_{05}$ = 55.6 ppm *$BMCL_{05}$ = 24.3 ppm*
	52.3	*2/10*	
	61.9	*6/10*	
	74	3/10	BMC_{01} = 60.8 ppm *BMC_{01} = 32.6 ppm*
	79	1/10	
	87	4/10	
	91	9/10	
	105	9/10	
30-minutes	12	0/10	LC_{50} = 21 ppm *LC_{50} = 13.5 ppm*
	12.6	*4/10*	
	13.4	*4/10*	
	**15	0/10	$BMCL_{05}$ = 12.6 ppm *$BMCL_{05}$ = 5.0 ppm*
	16	1/10	
	16.7	*10/10*	
	17	5/10	BMC_{01} = 10.7 ppm *BMC_{01} = 7.4 ppm*
	21.4	*9/10*	
	24	9/10	
1-hour	6.4	1/10	LC_{50} = 12 ppm *LC_{50} = 7.7 ppm*
	7.4	*4/10*	
	8.8	2/10	
	9.0	0/10	$BMCL_{05}$ = 7.8 ppm *$BMCL_{05}$ = 3.9 ppm*
	9.7	*9/10*	
	11.8	*10/10*	
	12	9/10	BMC_{01} = 9.8 ppm *BMC_{01} = 5.3 ppm*

* POD for 10-min AEGL-3

**POD for 30-min, 1-hr, 4-hr, and 8-hr AEGL-3

Pauluhn, 2006a

TABLE 1. Acute inhalation data for phosgene exposure in rats				
Exposure time (min)	LC_{50} **(ppm)**	LCt_{50} **(ppm•min)**	LC_{01} **(ppm)**	LCt_{01} **(ppm•min)**
10	62.5	625	26	260
30	13.5	402	7.2	216
60	7.7	462	5.2	312
240	2.1	504	1.3	312

TABLE 2. Acute lethality data in rats exposed to phosgene				
Concentration (ppm)	Exposure duration (min)	No. animals/sex	Mortality (rats)	
			M	F
41.1	10	5	2	1
44.8	10	5	0	0
52.3	10	5	1	1
61.9	10	5	3	3
12.6	30	5	3	1
13.4	30	5	3	1
16.7	30	5	5	5
21.4	30	5	5	4
0	60	5	0	0
7.4	60	5	2	2
9.7	60	5	5	4
11.8	60	5	5	5
2.2	240	5	5	1
2.7	240	5	5	4

Pauluhn, 2006b

Adult male Wistar rats; Nose-only; GLP inhalation study

30 min: 0.2, 0.5, 1.0, 2.0 or 4.0 ppm

240 minutes: to 0, 0.05, 0.1, 0.2, 0.4 or 1.0 ppm

Observed for up to 84 days post-exposure; Interim sacrifices for bronchoalveolar lavage (BAL) and lung weights.

No deaths occurred in any groups.

Histopathology on day 84 showed similar lesions between treated and control rats in the lungs,

At day 28 in the 1.0 ppm group (240 minutes), 5/6 rats had minimal to slight hypercellularity of the terminal bronchioles with occasional peribronchial inflammatory infiltrates and septal thickening.

There was no evidence of persistent inflammatory responses such as chronic pneumonia.

Statistically significant ($p<0.01$ or 0.05) increases in lung weight were observed in the rats treated with 4.0 ppm for 30 minute or $\geq$ 0.4 ppm for 240 minutes.

In the BAL fluid, protein levels and polymorphonuclear leukocytes (PMNs) increased starting on post-exposure day 1 in rats exposed to $\geq$ 2 ppm for 30 minutes and $\geq$ 0.2 ppm for 240 minutes.

By 7 days post-exposure, parameters were similar to those of controls except in the highest concentration animals (1.0 ppm x 240 minutes).

TABLE 4. Group means (±SD) of findings in rats exposed for 30 minutes to phosgene				
	Lung wt/body wt (mg/100g)	Protein in BAL (g/L)	Collagen in BAL (mg/L)	Neutrophilic granulocytes in BAL (%)
Day 1				
Control***	466.0 ± 13.9	0.194 ± 0.012	10.0 ± 2.7	0.111 ± 0.172
0.2	475.2 ± 25.2	0.169 ± 0.020	12.2 ± 2.1	0.056 ± 0.136
0.5	469.1 ± 11.0	0.181 ± 0.031	16.5 ± 4.8	0.111 ± 0.172
1.0	483.0 ± 26.5	0.271 ± 0.064	9.67 ± 3.37	0.500 ± 0.506
2.0	495.3 ± 21.6	0.685** ± 0.083	29.9* ± 4.2	1.44** ± 0.69
4.0	561.4** ± 34.1	2.24** ± 1.01	250.3** ± 229.2	8.00** ± 3.14
Day 3				
Control***	453.5 ± 15.8	0.190 ± 0.075	10.6 ± 1.8	0.222 ± 0.272
0.2	453.5 ± 11.9	0.184 ± 0.029	13.3 ± 1.9	0.278 ± 0.328
0.5	452.0 ± 10.4	0.184 ± 0.023	10.5 ± 3.4	0.056 ± 0.136
1.0	464.2 ± 6.1	0.190 ± 0.022	13.7 ± 3.0	0.056 ± 0.136
2.0	475.3 ± 19.6	0.252 ± 0.057	13.7 ± 6.0	2.39 ± 3.19
4.0	538.6** ± 31.7	0.349 ± 0.207	22.4 ± 16.9	7.22 ± 10.36
Day 7				
Control***	438.4 ± 16.5	0.163 ± 0.022	10.0 ± 5.3	0.222 ± 0.404
0.2	437.1 ± 27.3	0.197 ± 0.019	12.2 ± 3.6	0.611 ± 0.647
0.5	421.6 ± 15.7	0.198 ± 0.027	10.3 ± 4.6	0.111 ± 0.172
1.0	441.4 ± 22.7	0.196 ± 0.016	12.6 ± 2.2	0.167 ± 0.279
2.0	445.0 ± 12.7	0.169 ± 0.023	11.3 ± 2.5	0.222 ± 0.272
4.0	4..62 ± 11.4	0.174 ± 0.024	10.0 ± 4.9	0.278 ± 0.443
Day 28				
Control***	402.7 ± 12.0	0.223 ± 0.025	11.5 ± 3.2	0.278 ± 0.251
0.2	407.9 ± 19.6	0.218 ± 0.015	13.3 ± 4.7	0.389 ± 0.491
0.5	399.7 ± 18.2	0.210 ± 0.027	12.3 ± 4.9	0.167 ± 0.279
1.0	385.3 ± 15.4	0.195 ± 0.024	12.4* ± 2.9	0.278 ± 0.534
2.0	436.1* ± 12.4	0.206 ± 0.019	11.9 ± 3.7	0.444 ± 0.779
4.0	418.1 ± 20.1	0.206 ± 0.024	19.4 ± 4.2	0.167 ± 0.279
Day 84				
Control***	334.6 ± 17.2	0.243 ± 0.025	10.3 ± 2.5	0.278 ± 0.328
0.2	324.6 ± 13.7	0.298 ± 0.130	15.3 ± 5.1	0.056 ± 0.136
0.5	336.4 ± 12.8	0.248 ± 0.020	14.3 ± 4.8	0.056 ± 0.136
1.0	328.2 ± 15.7	0.236 ± 0.016	21.8** ± 5.0	0.056 ± 0.136
2.0	330.3 ± 10.9	0.289 ± 0.020	12.4 ± 2.6	0.200 ± 0.298
4.0	327.1 ± 9.8	0.262 ± 0.016	14.6 ± 2.7	0.167 ± 0.279

[a] Data from Pauluhn, 2006b.

* Statistically significant at $p<0.05$ or ** $p<0.01$*** Control (0 ppm) exposure was 4-hour duration.

TABLE 3. Group means (±SD) of findings in rats exposed for 4 hours to phosgene				
	Lung wt/body wt (mg/100g)	**Protein in BAL (g/L)**	**Collagen in BAL (mg/L)**	**Neutrophilic granulocytes in BAL (%)**
Day 1				
Control	466.0 ± 13.9	0.194 ± 0.012	10.0 ± 2.7	0.111 ± 0.172
0.1	479.2 ± 29.0	0.214 ± 0.037	13.7 ± 3.9	0.500 ± 0.459
0.2	521.3 ± 40.0	0.905* ± 0.690	61.5 ± 81.1	4.00** ± 1.52
0.4	571.5** ± 19.5	1.89** ± 0.65	141.7** ± 73.8	7.33** ± 3.80
1.0	1023.0** ± 162.0	13.6** ± 3.0	3203.0** ± 870	36.9** ± 7.4
Day 3				
Control	453.5 ± 15.8	0.190 ± 0.075	10.6 ± 1.8	0.222 ± 0.272
0.1	472.2 ± 14.8	0.179 ± 0.025	7.32 ± 3.00	0.167 ± 0.408
0.2	472.8 ± 21.2	0.216 ± 0.025	9.00 ± 1.75	0.444* ± 0.544
0.4	536.9** ± 18.8	0.378* ± 0.084	35.6** ± 15.5	5.83 ± 3.32
1.0	-	-	-	-
Day 7				
Control	438.4 ± 16.5	0.163 ± 0.022	10.0 ± 5.3	0.222 ± 0.404
0.1	429.0 ± 13.4	0.169 ± 0.008	9.97 ± 4.63	0.167 ± 0.183
0.2	432.6 ± 20.2	0.183 ± 0.029	11.9 ± 3.8	0.389 ± 0.328
0.4	464.3 ± 20.7	0.175 ± 0.026	14.2 ± 3.7	0.167 ± 0.279
1.0	627.8** ± 54.7	0.302 ± 0.082	49.3 ± 5.0	0.722* ± 1.611
Day 28				
Control	402.7 ± 12.0	0.223 ± 0.025	11.5 ± 3.2	0.278 ± 0.251
0.1	420.6 ± 20.7	0.204 ± 0.023	12.6 ± 3.8	0.111 ± 0.272
0.2	420.1 ± 16.9	0.183 ± 0.020	14.7 ± 3.2	0.111 ± 0.172
0.4	431.4* ± 9.2	0.212 ± 0.016	13.4* ± 1.8	0.222 ± 0.344
1.0	438.3* ± 15.8	0.195 ± 0.026	13.9 ± 1.8	0.000 ± 0.000
Day 84				
Control	334.6 ± 17.2	0.243 ± 0.025	10.3 ± 2.5	0.278 ± 0.328
0.1	321.8 ± 13.2	0.257 ± 0.008	15.6 ± 4.7	0.111 ± 0.272
0.2	324.0 ± 21.5	0.268 ± 0.032	21.4** ± 5.1	0.278 ± 0.251
0.4	320.6 ± 23.3	0.276 ± 0.024	10.2 ± 2.8	0.000 ± 0.000
1.0	-	-	-	-

[a] Data from Pauluhn, 2006b.

* Statistically significant at $p<0.05$ or ** $p<0.01$

Pauluhn, 2006c.

Male and female beagles

30 minute head-only exposure: 0 (5 dogs), 2.3, 4.1 or 8.8 ppm (4/group)

Sacrifice 24-hr post exposure

2.3 and 4.1 ppm: Signs of irritation: minor nasal discharge, salivation, and lacrimation

4.1 and 8.8 ppm: Elevated BAL PMNs

8.8 ppm:
Labored breathing, reddened conjunctiva/mucosa and vomitus and rales on day 1 post-exposure. Pulmonary fibrinous inflammation, epithelial necrosis, hemorrhages, intra-alveolar fibrin exudation, minimal to slight focal septal thickening and positive Sirius-red reaction, Lung edema

Zwart et al., 1990

TABLE 5. Acute lethality data in rats and mice exposed to phosgene						
Concentration (ppm)	**Exposure duration (min)**	**No. animals/sex**	**Mortality (rats)**		**Mortality (mice)**	
			M	**F**	**M**	**F**
12	10	5	0	0	0	0
36	10	5	0	0	0	0
74	10	5	3	0	0	2
79	10	5	1	0	1	3
87	10	5	2	2	4	3
91	10	5	4	5	5	5
105	10	5	5	4	5	5
12	30	5	0	0	0	5
15	30	5	0	0	1	0
16	30	5	1	0	4	5
17	30	5	2	3	4	5
24	30	5	5	4	2	3
6.4	60	5	0	1	2	4
8.8	60	5	0	2	3	5
9.0	60	5	0	0	3	5
12	60	5	4	5	4	5

Gross et al., 1965

Total of 118 male Wistar rats

Exposed to 0.5 to 4.0 ppm phosgene for 5 minutes to 8 hours

Exposures were varied to give CT products between 12 and 360 ppm-min

Exposure to high concentrations of phosgene (2 ppm for 90 min) produced chemical pneumonia

Exposure to lower concentrations produced "chronic pneumonitis."

TABLE 6. Summary of lethal animal inhalation studies with phosgene				
Concentration (ppm)	**Time**	**Species**	**Effect**	**Reference**
various	30 min	Dog	LC_{50} = 66 ppm	Boyland et al., 1946
various	30 min	Dog	LC_{50} = 61-70 ppm	Underhill, 1920
various	60 min	Dog	LC_{50} = 42 ppm	Boyland et al., 1946
various	8 min	Rat	LC_{50} = 92 ppm	Boyland et al., 1946
12, 37, 75, 80, 88, 93, or 106	10 min	Rat	LC_{50} = 82 ppm	Zwart et al., 1990
41, 44, 52, or 61	10 min	Rat	LC_{50} = 62 ppm	Pauluhn, 2006a
12, 15, 16, 17, or 25	30 min	Rat	LC_{50} = 21 ppm	Zwart et al., 1990
12, 13, 17, or 22	30 min	Rat	LC_{50} = 13.5 ppm	Pauluhn, 2006a
Various	32 min	Rat	LC_{50} = 17 ppm	Boyland et al., 1946
6.4, 8.8, 9.0 or 12	60 min	Rat	LC_{50} = 12 ppm	Zwart et al., 1990
7.3, 9.6, or 12	60 min	Rat	LC_{50} = 7.7 ppm	Pauluhn, 2006a
Various	64 min	Rat	LC_{50} = 11 ppm	Boyland et al., 1946
2.2 or 2.7	240 min	Rat	LC_{50} = 2.1 ppm	Pauluhn, 2006a
10, 15, 25, 35, 50, 70 or 90	5 min	Mouse	LC_{50} = 33 ppm	Kawai, 1973
Various	8 min	Mouse	LC_{50} = 77 ppm	Boyland et al., 1946
12, 37, 75, 80, 88, 93, or 106	10 min	Mouse	LC_{50} = 79 (m) and 60 (f) ppm	Zwart et al., 1990
12, 15, 16, 17, or 25	30 min	Mouse	LC_{50} = 19 (m) and 11.5 (f) ppm	Zwart et al., 1990
1.0, 2.0, 3.0, 6.0, 9.0 or 13.5	30 min	Mouse	LC_{50} = 5.1 ppm	Kawai, 1973
various	32 min	Mouse	LC_{50} = 15 ppm	Boyland et al., 1946
6.4, 8.8, 9.0 or 12	60 min	Mouse	LC_{50} = 9.5 (m) and 5.0 (f) ppm	Zwart et al., 1990
Various	64 min	Mouse	LC_{50} = 7 ppm	Boyland et al., 1946
Various	8 min	guinea pig	LC_{50} = 43 ppm	Boyland et al., 1946
Various	32 min	guinea pig	LC_{50} = 13 ppm	Boyland et al., 1946
Various	64 min	guinea pig	LC_{50} = 11 ppm	Boyland et al., 1946

TABLE 7. Summary of non-lethal animal inhalation studies with phosgene				
Concentration (ppm)	**Time**	**Species**	**Effect**	**Reference**
0 or 60	10 min	Pig	LOAEL ≥ 60 ppm, based on increased lung wet weight, mortality	Brown et al., 2002
137, 244, 435 or 773	10 min	sheep	LOAEL ≥ 137 ppm based on pulmonary edema, shallow breathing	Keeler et al., 1990a
0 or 490 to 611	10 min	sheep	LOAEL ≥ 490 ppm based on lung edema	Keeler et al., 1990b
0 or 8	20 min	mouse	LOAEL ≥ 8 ppm, based on acidosis, clinical signs and ↓ body wt., ↑ lung ww/dw	Sciuto et al., 2001
0 or 22	20 min	mouse, rat and guinea pig	LOAEL ≥ 22 ppm, based on ↑ LFP	Sciuto, 1998
0, 2.1, 4.3 or 8.8	30 min *dogs sacrificed 24-hr post-exposure	dog	LOAEL= 4.3 ppm, based on increased PMNs in BAL fluid NOAEL = 2.1 ppm	Pauluhn, 2006c
.2, .5, 1.0, 2.0 or 4.0	30 min	Rat	LOAEL = 2.0 ppm, based on clinical signs and ↓ body wt., ↑ LFP NOAEL = 1. 0 ppm	Pauluhn, 2006b
0.8, 0.9, 2.5, or 3	60 min	Rat	Moderate Pneumonitis	Gross et al., 1965
2	90 min	Rat	Chemical pneumonia	Gross et al., 1965
0, 0.05, 0.1, 0.2, 0.4 or 1.0	240 min	Rat	LOAEL = 0.2 ppm, based on based on clinical signs and ↓ body wt., ↑ LFP NOAEL = 0.1 ppm	Pauluhn, 2006b
0, 0.1, 0.5 or 1.0	240 min	Rat	LOAEL = 0.5 ppm based on decrease in NK cell activity NOAEL = 0.1 ppm	Burleson and Keyes, 1989
0 or 1.0	240 min	Rat	LOAEL ≥ 1.0 ppm based on ↓ body wt., ↑ lung wts	Ehrlich et al., 1989
0 or 0.5	240 min	Rat	LOAEL ≥ 0.5 ppm based on ↑ LFP and lung wts,	Jaskot et al., 1989
0, 0.25 or 0.5	240 min	Guinea pig	LOAEL ≥ 0.25 ppm based on ↑ LFP	Slade et al., 1989
0.1 to 0.5	240 min	mouse	LOAEL = 0.15 ppm based on ↑ phenobarbital induced sleeping times NOAEL = 0.10	Illing et al., 1988
0, 0.125, 0.25, 0.5 or 1.0	240 min	Rat	LOAEL = 0.25 ppm based on ↑ PMNs in lavage fluid NOAEL = 0.125 ppm	Currie et al., 1987a
0, 0.05, 0.125, 0.25, 0.5 or 1.0	240 min	Rat	LOAEL ≥ 0.05 ppm based on ↓ ATP in lungs	Currie et al., 1987b
0, 0.1, 0.2, 0.5 or 1.0	240 min	rat, mouse and hamster	LOAEL = 0.2 ppm based on ↑ LFP NOAEL = 0.1 ppm	Hatch et al., 1986
0, 0.1, 0.2, 0.5 or 1.0	240 min	rabbit and guinea pig	LOAEL = 0.5 ppm based on ↑ LFP NOAEL = 0.2 ppm	Hatch et al., 1986
0 or 1.0	240 min	Rat	LOAEL ≥ 1.0 ppm based on ↓ body wt., ↑ lung wts	Franch and Hatch, 1986
0 or 1.0	240 min	Rat	LOAEL ≥ 1.0 ppm based on ↑ pulmonary edema	Frosolono and Currie, 1985
0 or 1.0	420 min	Rat	LOAEL ≥ 1.0 ppm based on ↑ lung wts	Franch and Hatch, 1986
0.125 or 0.25	4 hrs/day, 5 days/week for 17 days	Rat	LOAEL = 0.25 ppm based on ↑ lung wts and ↑ NPSH and G6PD activity NOAEL = 0.125 ppm	Franch and Hatch, 1986
0, 0.1, 0.2, 0.5 or 1.0	0.1 ppm for 5 days/week; 0.2 ppm for 5 days/week; 0.5 ppm for 2 days/week; 1.0 ppm for 1 day/week 6 hrs/day for up to 12 weeks	Rat	LOAEL = 0.1 ppm based on reversible lung histopathology; ↑ lung displacement volume NOAEL = none	Kodavanti et al., 1997
0, 0.1, 0.2, or 0.5	0.1 and 0.2 ppm for 5 days/week; 0.5 ppm for 2 days/week 6 hrs/day for up to 12 weeks	Rat	LOAEL = 0.1 ppm based on decreased bacterial clearance after infection with *S. zooepiemicus* NOAEL = none	Selgrade et al., 1995

ATTACHMENT 9

AEGLs for MONOCROTOPHOS
(CAS Reg. No. 141-66-2)

NAC/AEGL Meeting 49
Research Triangle Park, NC
September 9-11, 2009

MONOCROTOPHOS

- organophosphate insecticide; cholinesterase (ChE) inhibitor

- no longer used in any registered pesticide products in the United States

Human Data

- No inhalation toxicity data

Animal Data
Lethality Data

Mortality in Rats Following Acute Inhalation Exposure to Monocrotophos		
Exposure (mg/m^3)	Comments	Source
1-hr LC_{50}: 94 4-hr LC_{50}: 80	♂ and ♀; 18 rats/group, 70.3% technical grade ♂ and ♀; 18 rats/group, 70.3% technical grade	Sachsse et. al. 1974
4-hr LC_{50}: 63	no details; original study unavailable	ACGIH, 2002
1-hr LC_{50}: 163 1-hr LC_{50}: 176	♂; 10 rats/group, 61-64% technical grade ♀; 10 rats/group, 61-64% technical grade	Newell and Dilley, 1978

Animal Data
Non Lethal Effects

- Newell and Dilley (1978): rats exposed 1 hr to monocrotophos (97 to 308 mg/m^3)
  - signs of cholinergic poisoning (lacrimation, salivation, defecation, muscle fasciculations)
  - neither exposure-response data nor severity/incidence data were provided
  - not stated which, if any, of the exposures were without lethality

AEGL 1

AEGL-1 values for monocrotophos					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Not recommended; insufficient data.

AEGL-2

AEGL-2 values for monocrotophos (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.32	0.22	0.17	0.15	0.073

- Exposure-response data are insufficient regarding an AEGL-2 critical effects and POD

- Assume steep exposure-response relationship by analogy to other OPs

- AEGL-2 values derived as 3-fold reduction of AEGL-3 values

AEGL-3

AEGL-3 values for monocrotophos (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.95	0.66	0.52	0.45	0.22

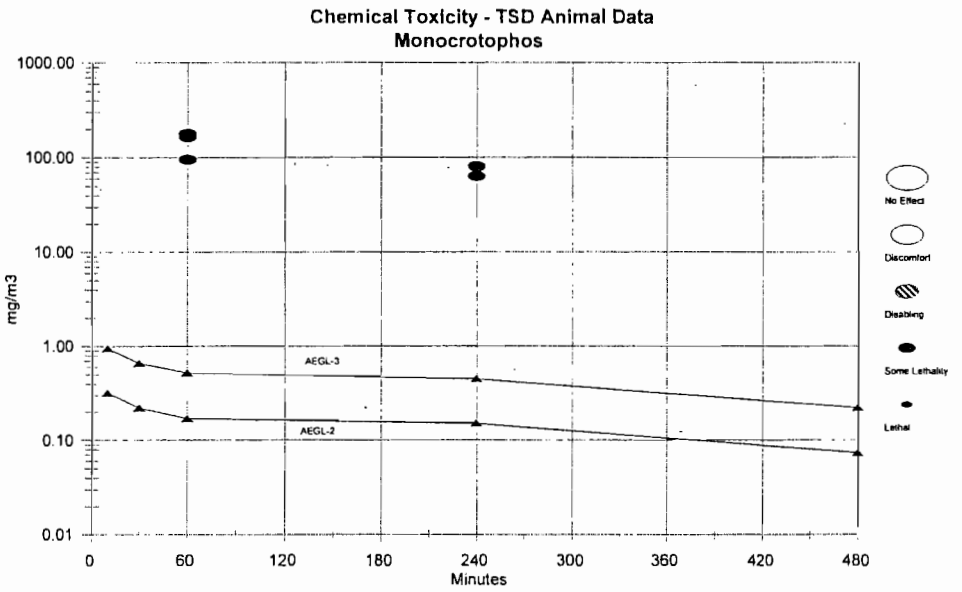
Key Study: Sachsse, K., Ullmann, G., Voss, G., Hess, R. 1974. Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Duncan,W.A.M., ed. Experimental Model Systems in Toxicology and Their Significance in Man. Proceedings of the European Society for the Study of Drug Toxicity. XV: 239-251.

Critical Effect/POD: Lethality threshold estimated as a 3-fold reduction of the 1-hour and 4-hour rat LC_{50} values of 94 mg/m^3 and 80 mg/m^3 (31.3 and 26.7 mg/m^3 respectively)

Time Scaling: Default exponents of $n = 3$ applied for extrapolating to shorter time points; $n = 1$ applied for extrapolating to longer exposure durations

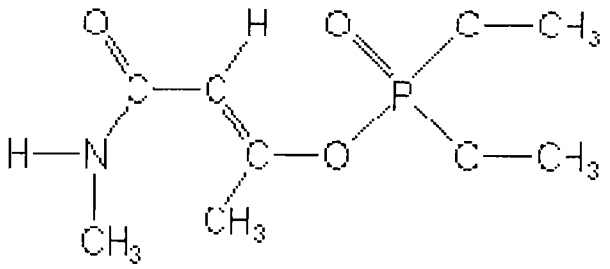
Uncertainty Factors: Total UF = 30
Interspecies: 3; The underlying mechanism of organophosphate toxicity is similar across species; additionally, humans may have some protective advantage due higher plasma ChE and red blood cell ChE activity which are less critical targets and may serve as a buffer against OP-mediated cholinergic toxicity.

Intraspecies: 10; due to known genetic polymorphisms in activity levels of enzymes involved in deactivation of OPs as well as gender and age-related variability in the toxic response to organophosphates.

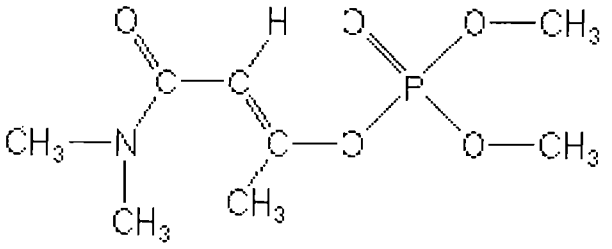


Comparison of Proposed AEGL Values for Monocrotophos and Dicrotophos (expressed as mg/m^3)

Classification	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1					
Monocrotophos	NR	NR	NR	NR	NR
Dicrotophos	NR	NR	NR	NR	NR
AEGL-2					
Monocrotophos	0.32	0.22	0.17	0.15	0.073
Dicrotophos	0.17	0.17	0.17	0.17	0.083
AEGL-3					
Monocrotophos	0.95	0.66	0.52	0.45	0.22
Dicrotophos	0.50	0.50	0.50	0.50	0.25



Monocrotophos



Dicrotophos

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHAMIDOPHOS

National Advisory Committee for AEGLs Meeting 49
Research Triangle Park, NC
September 9-11, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Henry Anderson

Chemical Reviewers:
Paul Tobin
Robert Benson

ATTACHMENT 10

4-hour study with male and female rats (Pauluhn 1986)

Concentration (mg/m^3)	Effect
11.4	No clinical signs, no mortality
24.3	No clinical signs, no mortality
45.0	Tremor, reduced motility, no mortality
195.5	Clinical signs, mortality 3/10
241.7	Clinical signs, mortality 8/10
350.3	Clinical signs, 9/10

Properties

Organophosphate pesticide
Liquid; low vapor pressure

Data Base

Human studies: no data
Acute aerosol studies with rats
Lethality studies performed in two different laboratories showed diverse results
- Indicate difficulty in sampling and measuring aerosol
- rat: 4-hour LC_{50} of 63.2-76.5 mg/m^3 (Sangha 1984)
- rat: 4-hour LC_{50} of 213 mg/m^3 (Pauluhn 1986)

Non-lethal, 5-day repeat-exposure study (Pauluhn 1986):
- 1.4, 5.4 mg/m^3: no clinical signs; no plasma, erythrocyte, or brain ChE inhibition
- 33.1 mg/m^3: slight tremor following exposure; brain ChE 33% of control value.

Oral studies: genotoxicity, carcinogenicity, reproductive/developmental results negative

Metabolism

Oral studies only
Rapidly absorbed, distributed to tissues, metabolized, and excreted
Metabolized ultimately to phosphoric acid and CO_2
Metabolized primarily by hydrolysis; not by A-esterases or carboxylesterases, enzymes that show age-related differences (Moser 1999; Padilla et al. 2000)
Considered non-cumulative
~80% of a near-lethal intravenous dose to rats (8 mg) excreted within 24 hours
- cholinergic signs peaked at 20-60 minutes
- correlated with AChE activity inhibition in the brain (15-20% of control)

Rat brain and plasma ChE spontaneously reactivated *in vitro*

Mode of Action

Cholinesterase activity inhibition
- Erythrocyte acetylcholinesterase activity inhibition biomarker for nervous system
- Sustained action of neurotransmitter acetylcholine
- Plasma cholinesterase is butyl or pseudocholinesterase

Signs and symptoms of acetylcholinesterase activity inhibition
- Tremor, staggering, reduced motility, dyspnea…

Uncertainty Factors

Modifying factor: 2

Interspecies uncertainty factor: 3
Rats and humans rapidly metabolize methamidophos

Intraspecies uncertainty factor: 3
No difference in sensitivity between adult and juvenile rats (oral study)

Total modifying/uncertainty factor: 20

Time-scaling

No time-scaling information

Choice of Study

Pauluhn (1986) study showed consistency in dose-response data; measured values correlated with nominal values

Data for Derivation of AEGL-1

Study: Pauluhn 1986

Endpoint: No clinical signs in rat at 11.4 mg/m^3 for 4 hours

Although this endpoint is below the definition of an AEGL-1, the next higher exposure of 24.1 mg/m^3 was used as the AEGL-2 because the next higher exposure after that was the threshold for mortality (45 mg/m^3)

Time-scaling: $C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations

AEGL-1 Values for Methamidophos				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
1.1 mg/m^3	1.1 mg/m^3	0.90 mg/m^3	0.57 mg/m^3	0.29 mg/m^3

Data for Derivation of AEGL-2

Study: Pauluhn 1986

Endpoint: No clinical signs in rat at 24.3 mg/m^3 for 4 hours

Although this endpoint is below the definition of an AEGL-2, the next higher exposure of 45 mg/m^3 was the threshold for mortality

Time-scaling: $C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations

AEGL-2 Values for Methamidophos				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
2.4 mg/m^3	2.4 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	0.61 mg/m^3

Data for Derivation of AEGL-3

Study: Pauluhn 1986

Endpoint: 4-hour $BMCL_{05}$ of 56.27 mg/m^3
(BMC_{01} was 101.54 mg/m^3)

Time-scaling: $C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations

AEGL-3 Values for Methamidophos				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
5.6 mg/m^3	5.6 mg/m^3	4.5 mg/m^3	2.8 mg/m^3	1.4 mg/m^3

METHAMIDOPHOS

Proposed AEGL Values for Methamidophos					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	1.1 mg/m^3	1.1 mg/m^3	0.90 mg/m^3	0.57 mg/m^3	0.29 mg/m^3
AEGL-2	2.4 mg/m^3	2.4 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	0.61 mg/m^3
AEGL-3	5.6 mg/m^3	5.6 mg/m^3	4.5 mg/m^3	2.8 mg/m^3	1.4 mg/m^3

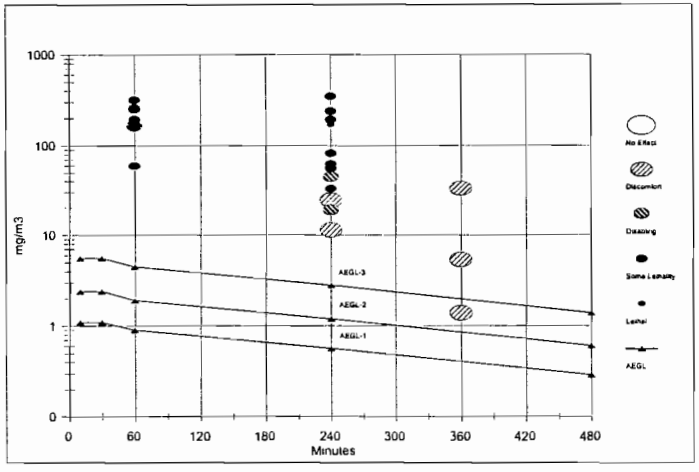
All endpoints based on Pauluhn (1986)

AEGL-1: 4-hour exposure of rats to 11.4 mg/m^3
AEGL-2: 4-hour exposure of rats to 24.3 mg/m^3
AEGL-3: 4-hour $BMCL_{05}$ for rats of 56.27 mg/m^3

Time scaling used default values of n = 3 and 1 for shorter and longer exposure durations, respectively.

METHAMIDOPHOS

Category graph of toxicity data and AEGL values



ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)
FOR
MEVINPHOS
(CAS Reg. No. 7786-34-7)

NAC/AEGL-49
September 9-11, 2009

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Daniel Sudakin

Chemical Reviewers: Paul Tobin, Jim Holler

ATTACHMENT 11

Mevinphos

Common Synonyms: Phosdrin, Crotonic acid,

Conversion
1 ppm= 9.17 mg/m^3
1 mg/m^3= 0.11 ppm

Physical Characteristics:
- Liquid-pale yellow-orange
- **Vapor Pressure – 1.28 x 10^{-4} mm HG @ 20°C**

Uses:
- Organophosphate pesticide

Issues
Extremely limited data
No new data available
Low vapor pressure likely precludes significant inhalation exposure
Explore route-to-route extrapolation

Uncertainty Factors

Interspecies 3- variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as mevinphos than do other species. This decreases the dose to critical targets.

Intraspecies 10- the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

ANIMAL DATA

Species	Concentration (ppm)	Exposure Time	Effect	Ref.
Rat	0.012 mg/L 1.32 ppm 0.0073 mg/L 0.80 ppm 0.0098 mg/L 1.08 ppm	4 hr	Male LC_{50} Female LC_{50} Combined LC_{50}	U.S. EPA 1999
Rat	9.8 mg/m^3 1.078 ppm 8-10 ppm	1 hr	LC_{50}	ACGIH 2003
Rat	0.053 mg/L 5.83 ppm 0.087 mg/L 9.57 ppm 0.130 mg/L 14.3 ppm 0.173 mg/L 19 ppm 0.346 mg/L 38 ppm	1 hr	17% mortality 33% mortality 50% mortality 50% mortality 100% mortality	Kodama et al. 1954
Rat	0.24 mg/L 26.64 ppm	Up to 1 hr	10-15 min- miosis, ear twitching, ↑ chewing 15-40 min- lacrimation, salivation, tremors 40-60 min- respiratory distress, convulsions, death	Kodama et al. 1954

AEGL-1 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

AEGL-1 values were not derived due to insufficient data. Absence of an AEGL-1 value does not imply that exposure below the AEGL-2 concentration is without adverse effects.

AEGL-2 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.037 ppm (0.34 mg/m^3)	0.026 ppm (0.24 mg/m^3)	0.021 ppm (0.20 mg/m^3)	0.0053 ppm (0.049 mg/m^3)	0.0026 ppm (0.024 mg/m^3)

Key Study: Kodama, J.K., M.S Morse, H.H. Anderson, M.K. Dunlap, and C.H. Hine. 1954. Comparative toxicity of two vinyl-substituted phosphates. Arch. Ind. Hyg. Occup. Med. 9: 45-61

Organophosphate poisoning exhibits a steep exposure-response curve (NRC 2003). One of six rats died after a 1 hour exposure to 5.83 ppm, and all rats died after exposure to 38 ppm of mevinphos (Kodama et al. 1954).

Rationale: In the absence of empirical data, and in accord with AEGL derivation guidelines for chemicals with steep dose-response curves (NAS 2001), the AEGL-2 values for mevinphos were set at one-third of the AEGL-3 values.

AEGL-3 Values for Mevinphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.11 ppm (1.0 mg/m^3)	0.079 ppm (0.72 mg/m^3)	0.062 ppm (0.57 mg/m^3)	0.016 ppm (0.15 mg/m^3)	0.0078 ppm (0.072 mg/m^3)

Key Study: Kodama, J.K., M.S Morse, H.H. Anderson, M.K. Dunlap, and C.H. Hine. 1954. Comparative toxicity of two vinyl-substituted phosphates. Arch. Ind. Hyg. Occup. Med. 9: 45-61

Toxicity endpoint: The AEGL-3 values were based upon the 1-hr $BMCL_{05}$ of 1.87 ppm (17 mg/m^3) used as an estimate of lethality threshold in rats.

Time scaling: $C^n \times t = k$, n = 3 or 1

Uncertainty factors: A total uncertainty factor of 30 was applied to
Interspecies: 3; variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as mevinphos than do other species. This decreases the dose to critical targets.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

Summary of AEGL Values for Mevinphos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.037 ppm (0.34 mg/m^3)	0.026 ppm (0.24 mg/m^3)	0.021 ppm (0.20 mg/m^3)	0.0053 ppm (0.049 mg/m^3)	0.0078 ppm (0.071 mg/m^3)
AEGL-3 (Lethal)	0.11 ppm (1.0 mg/m^3)	0.079 ppm (0.72 mg/m^3)	0.062 ppm (0.57 mg/m^3)	0.016 ppm (0.15 mg/m^3)	0.0078 ppm (0.072 mg/m^3)

NR. Not Recommended Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	**0.037 ppm (0.34 mg/m^3)**	**0.026 ppm (0.24 mg/m^3)**	**0.021 ppm (0.20 mg/m^3)**	**0.0053 ppm (0.049 mg/m^3)**	**0.0078 ppm (0.071 mg/m^3)**
AEGL-3	**0.11 ppm (1.0 mg/m^3)**	**0.079 ppm (0.72 mg/m^3)**	**0.062 ppm (0.57 mg/m^3)**	**0.016 ppm (0.15 mg/m^3)**	**0.0078 ppm (0.072 mg/m^3)**
PEL-TWA (OSHA)					0.01 ppm (skin) 0.1 mg/m^3
PEL-STEL (OSHA)	0.03 ppm (skin) 0.3 mg/m^3				
IDLH (NIOSH)		4 ppm 37 mg/m^3			
REL-TWA (NIOSH)					0.01 ppm (skin) 0.1 mg/m^3
REL-STEL (NIOSH)	0.03 ppm (skin) 0.3 mg/m^3				
TLV-TWA (ACGIH)					0.01 ppm 0.1 mg/m^3 (skin, IFV)
MAK (Germany)					0.01 ppm (skin) 0.1 mg/m^3
MAC- The Netherlands					0.01 ppm 0.1 mg/m^3

ACUTE EXPOSURE GUIDELINE LEVELS FOR PHOSPHAMIDON

National Advisory Committee for AEGLs Meeting 49
Research Triangle Park, NC
September 9-11, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Ed Bernas

Chemical Reviewer:
Susan Ripple

PHOSPHAMIDON

Properties
Organophosphate pesticide
Liquid; low vapor pressure

Data Base
Human studies: no data
Acute aerosol studies with rats, mice, and guinea pigs
All acute studies performed in same laboratory (Sachsse et al. 1974; 1980)
- rat: 4-hour LC_{50} of 135 mg/m^3
- mouse: 4-hour LC_{50} of <30 mg/m^3
- guinea pig: 4-hour LC_{50} of 1300 mg/m^3

Repeat-exposure study, 42 days, 4 hours/day (Battelle Institute 1965)
- rat: 0.5 mg/m3 resulted in "temporary inhibition of erythrocyte cholinesterase"

Subchronic study, 6 hours/day (Industrial Bio-Test Laboratories, Inc. 1964)
- rat, guinea pig, beagle dog: no effect at 125 mg/m^3

Genotoxicity and oral carcinogenicity studies: not genotoxic or carcinogenic
Oral developmental/reproductive studies with rats, mice, rabbits: not teratogenic

Metabolism
Oral studies only
Metabolized by oxidation, hydrolysis (by esterases), and glutathione conjugation
Considered non-cumulative

Mode of Action
Cholinesterase activity inhibition
- Erythrocyte acetylcholinesterase activity inhibition biomarker for nervous system
  - Sustained action of neurotransmitter acetylcholine
- Plasma cholinesterase is butyl or pseudocholinesterase

Glutathione-S-transferase depletion in mouse brain

Signs and symptoms of acetylcholinesterase activity inhibition
- Not described in inhalation studies
- Oral studies: tremors, ataxia, salivation, emesis....

Modifying/Uncertainty Factors

Modifying factor: 2 based on sparse data base and conflicting data

Interspecies uncertainty factor: 3
- Rat was intermediate in sensitivity to mouse and guinea pig

Intraspecies uncertainty factor: 10
- No chemical-specific data on human variability

Total modifying/uncertainty factor: 60

Higher modifying/uncertainty factors conflict with the repeat-exposure data

Time-scaling

No time-scaling information

Data for Derivation of AEGL-1

No data available
AEGL-1 values not recommended

AEGL-1 Values for Phosphamidon				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
NR	NR	NR	NR	NR

NR = Not recommended.

Data for Derivation of AEGL-2

No data available
Divide AEGL-3 values by 3

AEGL-2 Values for Phosphamidon				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
0.50 mg/m^3	0.50 mg/m^3	0.40 mg/m^3	0.25 mg/m^3	0.13 mg/m^3

Values supported by 42-day repeat exposure study (Battelle Institute 1965)
Temporary inhibition of erythrocyte cholinesterase activity in rats inhaling 0.5 mg/m^3, 4 hours/day, 5 days/week.

Data for Derivation of AEGL-3

Rat considered the more representative species

4 hour whole-body inhalation with rats (Sachsse et al. 1980)
LC_{50} value of 135 mg/m^3 (C.L. of 113-170 mg/m^3); no further data

Non-lethal concentration = LC_{50} value divided by 3 (Rusch et al. 2009)
Total adjustment/modifying/uncertainty factor = 180 (2x3x3x10)

AEGL-3 Values for Phosphamidon				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
1.5 mg/m^3	1.5 mg/m^3	1.2 mg/m^3	0.75 mg/m^3	0.38 mg/m^3

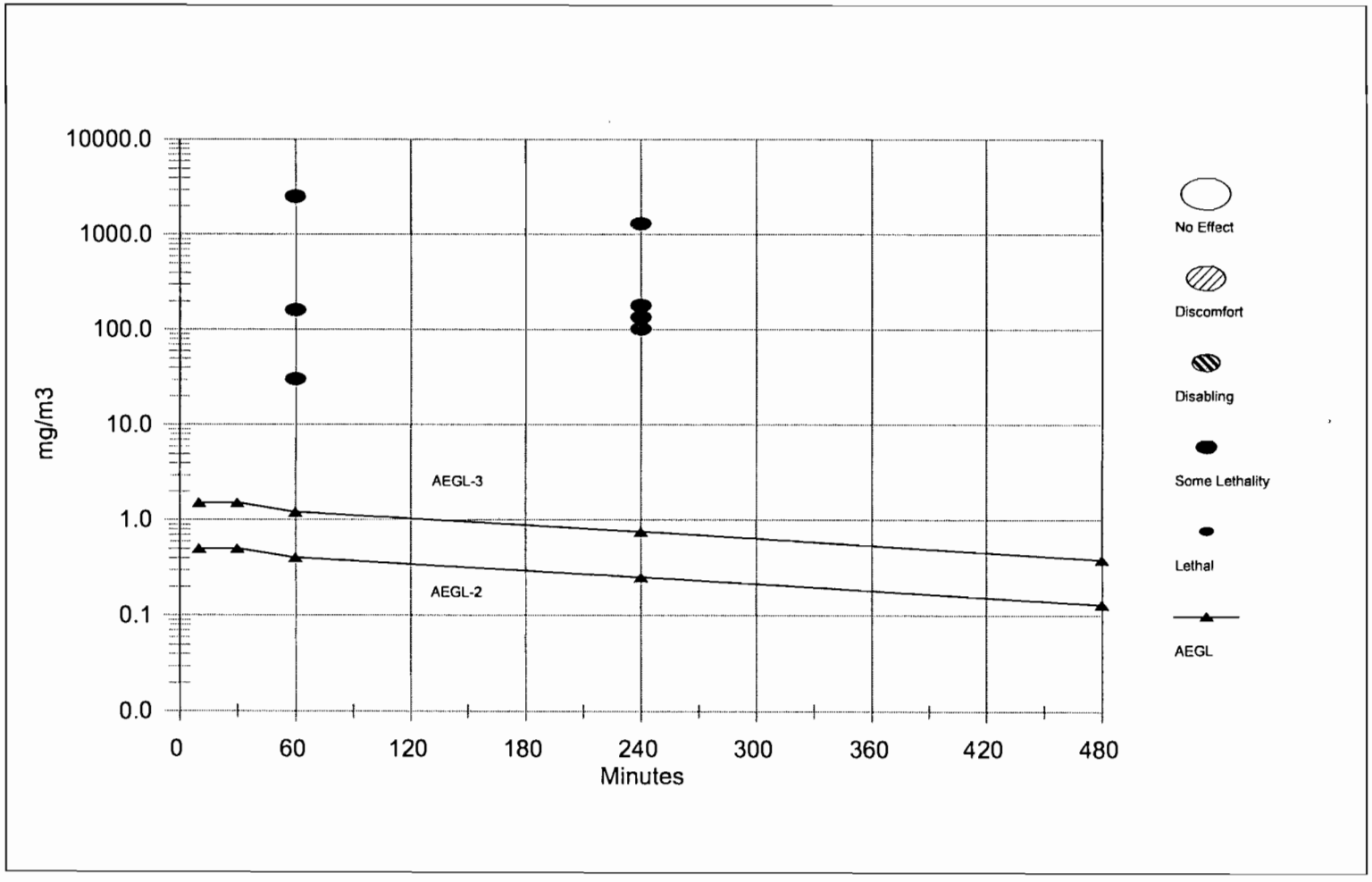
Proposed AEGL Values for Phosphamidon					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.50 mg/m^3	0.50 mg/m^3	0.40 mg/m^3	0.25 mg/m^3	0.13 mg/m^3
AEGL-3	1.5 mg/m^3	1.5 mg/m^3	1.2 mg/m^3	0.75 mg/m^3	0.38 mg/m^3

AEGL-1: In absence of suitable data, AEGL-1 values are not recommended.
AEGL-2: The AEGL-2 values were derived by dividing the AEGL-3 values by 3.
AEGL-3: Based on threshold for lethality – the 4-hour LC_{50} divided by 3

Time scaling used default values of n = 3 and 1 for shorter and longer exposure durations, respectively.

PHOSPHAMIDON

Category graph of toxicity data and AEGL values



ATTACHMENT 13

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR FENAMIPHOS (CAS Reg. No. 22224-92-6)

NAC/AEGL-49
September 9-11, 2009

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: George Woodall

Chemical Reviewers: Paul Tobin, Jim Holler

Fenamiphos

Common Synonyms: Nemacur, Phenamiphos,

Conversion
1 ppm= 12.4 mg/m^3
1 mg/m^3= 0.08 ppm

Physical Characteristics:
- Solid-white crystals
- Vapor Pressure – 1 x 10^{-7} mm Hg @25°C

Uses:
- Organophosphate pesticide- no longer used in the U.S.

Uncertainty Factors

Interspecies 3- variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as mevinphos than do other species. This decreases the dose to critical targets.

Intraspecies 10- the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

ANIMAL DATA- Inhalation

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat male	2.32 6.00 6.96 8.24 11.2 13.2 14.96 8.8	1 hr	No effect 5% mortality; (1/20) 30% mortality, (6/20) 60% mortality; (12/20) 65% mortality; (13/20) 95% mortality; (19/20) 100% mortality; (20/20) LC_{50}	Kimmerle 1972
Rat female	2.32 5.60 8.40 9.36 11.84 13.6 14.8 15.6 25.6 12	1 hr	No effect Cholinesterase activity inhibition 5% mortality; (1/20) Cholinesterase activity inhibition 35% mortality; (7/20) 60% mortality; (12/20) 90% mortality; (18/20) 90% mortality; (18/20) 100% mortality; (20/20) LC_{50}	Kimmerle 1972
Rat male	6.64 9.52 11.6 11.85 20 10.5	1 hr	Cholinesterase activity inhibition 20% mortality, (2/10) 60% mortality, (6/10) 90% mortality, (9/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat female	6.64 9.52 11.6 11.85 20 10.4	1 hr	Cholinesterase activity inhibition Cholinesterase activity inhibition 70% mortality, (7/10) 90% mortality, (9/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat male	4.56 4.96 8.0 12.4	4 hr	Cholinesterase activity inhibition Cholinesterase activity inhibition 60% mortality, (6/10); LC_{50} 100% mortality, (10/10)	Thyssen 1979a
Rat female	4.56 4.96 8.0 12.4 15.28	4 hr	Cholinesterase activity inhibition 10% mortality, (1/10) 50% mortality, (5/10); LC_{50} 90% mortality, (9/10) 100% mortality, (10/10)	Thyssen 1979a
Rat	8	4 hr	Less than the LC_{50}	U.S. EPA 1999

AEGL-1 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

No AEGL-1 values were established because the AEGL-1 values were too close to or exceeded AEGL-2 values.

AEGL-1

10-minute	30-minute	1-hour	4-hour	8-hour
0.11 ppm (1.4 mg/m^3)	0.089 ppm (1.1 mg/m^3)	0.077 ppm (0.95 mg/m^3)	0.058 ppm (0.72 mg/m^3)	0.05 ppm (0.62 mg/m^3)

Key Study: Kimmerle, G. 1972. Acute inhalation toxicity study with Nemacur active ingredient on rats. Unpublished report. Bayer AG, Wuppertal, Germany.

Toxicity endpoint: Male and female rats exposed to 2.32 ppm for 1 hour did not exhibit any effects of toxicity.

Time scaling: $C^n \times t = k$, where $n = 4.8$.

Uncertainty factors:
Interspecies: 3; variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as fenamiphos than do other species. This decreases the dose to critical targets.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

AEGL-2 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.080 ppm (0.99 mg/m^3)	0.063 ppm (0.78 mg/m^3)	0.053 ppm (0.66 mg/m^3)	0.040 ppm (0.50 mg/m^3)	0.037 ppm (0.46 mg/m^3)

Key Study: Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.

Data were insufficient for empirical derivation of AEGL-2 values for fenamiphos. Organophosphate poisoning exhibits a steep exposure-response curve (NRC 2003). One of twenty male rats died after exposure to 6.0 ppm, 6/20 died after exposure to approximately 7.0 ppm, and 12/20 died after exposure to 8.24 ppm. All 20 rats died after exposure to 14.96 ppm (Kimmerle 1972). In a study by Thyssen (1979a), 2/10 male rats died after exposure to 9.52 ppm for 1 hour, 6/10 died after exposure to 11.6 and 9/10 died after exposure to 11.85 ppm. Female rats had 70% mortality at 11.6 ppm and 90% mortality after exposure to 11.85 ppm for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 8.0 ppm and 100% mortality at 12.4 ppm, and female rats experienced 50% mortality at 8.0 ppm, 90% mortality at 12.4 ppm, and 100% mortality at 15.28 ppm. The lack of experimental data and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC 2001).

AEGL-3 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
0.24 ppm (3.0 mg/m^3)	0.19 ppm (2.4 mg/m^3)	0.16 ppm (2.0 mg/m^3)	0.12 ppm (1.5 mg/m^3)	0.11 ppm (1.4 mg/m^3)

Key Study: Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.

Toxicity endpoint: 4-hr $BMCL_{05}$ of 3.7 ppm used as an estimate of lethality threshold in female rats.

Time scaling: $C^n \times t = k$, where $n = 4.8$.

Uncertainty factors:
Interspecies: 3; variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as fenamiphos than do other species. This decreases the dose to critical targets.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.

Summary of AEGL Values for Fenamiphos

	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Non-disabling)	**NR**	**NR**	**NR**	**NR**	**NR**
AEGL-2 (Disabling)	**0.080 ppm (0.99 mg/m^3)**	**0.063 ppm (0.78 mg/m^3)**	**0.053 ppm (0.66 mg/m^3)**	**0.040 ppm (0.50 mg/m^3)**	**0.037 ppm (0.46 mg/m^3)**
AEGL-3 (Lethal)	**0.24 ppm (3.0 mg/m^3)**	**0.19 ppm (2.4 mg/m^3)**	**0.16 ppm (2.0 mg/m^3)**	**0.12 ppm (1.5 mg/m^3)**	**0.11 ppm (1.4 mg/m^3)**

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.

Extant Standards and Guidelines

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	**0.080 ppm (0.99 mg/m^3)**	**0.063 ppm (0.78 mg/m^3)**	**0.053 ppm (0.66 mg/m^3)**	**0.040 ppm (0.50 mg/m^3)**	**0.037 ppm (0.46 mg/m^3)**
AEGL-3	**0.24 ppm (3.0 mg/m^3)**	**0.19 ppm (2.4 mg/m^3)**	**0.16 ppm (2.0 mg/m^3)**	**0.12 ppm (1.5 mg/m^3)**	**0.11 ppm (1.4 mg/m^3)**
REL-TWA (NIOSH)[f]					0.008 ppm 0.1 mg/m^3 (skin)
TLV-TWA (ACGIH)[g]					0.004 ppm 0.05 mg/m^3 (IFV, skin)
MAC-Peak Category (The Netherlands)[k]					0.008 ppm 0.1 mg/m^3

ACUTE EXPOSURE GUIDELINE LEVELS FOR AUTOMOTIVE GASOLINE (UNLEADED)

National Advisory Committee for AEGLs Meeting 49
Research Triangle Park, NC
September 9-11, 2009

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Managers:
John Hinz
Calvin Willhite

Chemical Reviewers:
George Woodall
Ralph Gingell

GASOLINE
- Context -

Frame of reference – previous AEGL risk assessments

Jet Fuel

Complex hydrocarbon mixture

AEGL assessment base on *whole fuel*, not a subset of constituents

Time:	10'	30'	1 hr	4 hrs	8 hrs	end point
AEGL:			(mg/m^3)			
I – mild	←		290		→	RD_{50}
II – moderate	←		1100		→	"woe" 6 studies
III – death	←		ND		→	no data

Toluene

AEGL:			(mg/m^3)			
I – mild	←		750		→	<notable discomfort
II – moderate	←		4500		→	NOAEL, narcosis (rat)
III – death	←		16,900		→	lethal threshold (rat)

Xylenes

AEGL:			(mg/m^3)			
I – mild	←		560		→	eye irritation
II – moderate	←		4000		→	incoordination (rat)
III – death	←		10,800		→	lethal threshold (rat)

GASOLINE
- Issues -

Identification of Issues

- Base assessment on whole fuel vs. most volatile sunset of components ?
  - All constituents volatile (VP = 220/675 mm) → all evaporate → ***whole fuel***
- Representative Mol Wt for mixture – one value vs. many ?
  - 73 for "light ends" *vs.* 80 for "vapor" *vs.* 114 for "octane" → 108 average
  - 1.56 fold impact on conversion mg/m^3 → ppm . . . . . 108→ 4.42
- CAS No. ?
  - 86290-86-5 *vs.* 8006-61-9 *vs.* "mixture"

Uptake / Metabolism / Toxicity Issues

- Lipophilic solvents → quickly reach steady state blood & tissue → time scaling
- Component toxicity additive … P450 competition
- Inhalation toxicity low … acute endpoint usually narcosis

GASOLINE
- Properties -

Volatile and flammable liquid at ambient temperature

Whole gasoline: C_3-C_{11} hydrocarbons

Vapor: C_4-C_6 hydrocarbons

VP: 275 – 475 mm Hg @ 20°C

Defined as

Complex mixture of hydrocarbons consisting of paraffins, cycloparaffins, aromatic and olefinic hydrocarbons with carbon numbers predominantly in the C_3 to C_{11} range.

Complex substance made by blending various refinery streams with many hydrocarbon components.

Representative mol wt: 73 - 114

Contains various additives of low volatility compared with LMW hydrocarbons

MTBE – methyl *t*-butyl ether
TAME – *t*-amyl methyl ether
ETBE – ethyl *t*-butyl ether
TBA - *t*-butyl alcohol
EtOH – ethanol
etc….

GASOLINE
- Data Base -

Clinical Studies:

Older studies: no details

Drinker et al. (1943):
4-minute to 8 hour studies with whole gasoline and gasoline vapor. Does not meet U.S. EPA ethical standards

Davis et al. (1960): (wholly vaporized gasoline….)
30-minute exposures to three blends of gasoline vapor - conjunctival eye irritation measured photographically; graded +1 to +4
200 ppm (600 mg/m^3):
very slight eye irritation (+1) in two of three exposures; (-4) in third exposure
500 ppm (1500 mg/m^3):
very slight eye irritation (+1 [highest score]) in all three exposures
1000 ppm (3000 mg/m^3):
slight to intermediate eye irritation (+1 and +2); one subject graded +3 in one of three exposures, but reported no subjective eye irritation

GASOLINE
- Data Base -

Laboratory Animal Studies

Acute (4-hour) studies with the rat at the limit concentration of 5000 mg/m^3 vapor
No toxicologically significant effects
No difference in toxicity among blended streams

Repeat-exposure vapor studies with rats (1500 mg/m^3) and mice (6168 mg/m^3)
No toxicologically significant effects

Subchronic studies with rat:
Rat : 20,000 and 22,500 mg/m^3 vapor distilled at 154°F (Schreiner et al. 2000)
Monkey: 6350 mg/m^3 wholly vaporized gasoline (Kuna and Ulrich 1984)
✓ No toxicologically significant effects

Chronic toxicity/Carcinogenicity study with the rat:
20,000 mg/m^3 vapor (Benson et al. 2004)
✓ Survival unaffected; neuropathology unaffected; transient change in activity

Developmental/Reproductive toxicity 20,000 mg/m^3 vapor:
✓ Generally negative; ↓ weight gain of dams

Genetic toxicity assays: generally negative

GASOLINE

Metabolism

No study on mixtures
Individual components metabolized by cytochrome P-450/2E1
PBPK models use a lumped approach; components are competitively inhibited
i.e., additive…..

Mode of Action

Slightly irritating - contact eye and nose irritation
Central nervous system depression (narcosis)
lipophilic chemicals partition into neuronal membranes and myelin
disrupt ability of neurons to propagate action potential and repolarize

GASOLINE

Uncertainty Factors

Interspecies uncertainty factor: 1
No data on species variability; no sensitive species apparent
Higher blood:air partition coefficients for rats and mice = greater uptake
i.e., higher blood concentration → higher target tissue concentration than humans

Intraspecies uncertainty factor: 3
For chemicals with anesthetic action, the minimum alveolar concentration differs approximately 3-fold among humans

Total uncertainty factor: 3

Higher modifying/uncertainty factors conflict with the subchronic and chronic data

Time-scaling

No time-scaling information
Many volatile hydrocarbons approach steady-state in the blood within 2 hours

GASOLINE

Data for Derivation of AEGL-1

Key Study: Davis et al. 1960

Point of departure: slight eye irritation during a 30-minute exposure to 3000 mg/m^3

Interspecies uncertainty factor: not applicable
Intraspecies uncertainty factor: 3, subjective and objective eye irritation did not vary greatly among the tested subjects

Time-scaling: Not applicable; there is adaptation to the slight eye irritation that defines the AEGL-1.

AEGL-1 Values for Automotive Gasoline				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1000 mg/m^3	1000 mg/m^3	1000 mg/m^3	1000 mg/m^3	1000 mg/m^3

Support: no toxicologically significant effects were observed in rats exposed to 5000 mg/m^3 for 4 hours.

GASOLINE

Data for Derivation of AEGL-2

Consideration: Human study: Davis et al. (1960) – concentrations not high enough to cause narcosis.
Acute rodent studies: no effect in rat during 4-hour exposure to 5000 mg/m^3

Key Study: Schreiner et al. 2000

Point of departure: NOAEL for neurotoxicity (no tremors, ataxia, lethargy) in rats exposed to 22,500 mg/m^3 for 6 hours/day, 5 days/week for 90 days. Although this endpoint may be below the definition of an AEGL-2, no higher concentrations were tested.

Uncertainty factors
Interspecies: 1, higher blood:air partition coefficients in rodents for many hydrocarbons
Intraspecies: 3, the minimum alveolar concentration for narcosis due to solvent inhalation differs approximately 3-fold among individuals.

Time-scaling: none, but could be applied

AEGL-2 Values for Automotive Gasoline				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *

***The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.**

GASOLINE

Data for Derivation of AEGL-3

No studies with measured concentrations addressed the threshold for lethality.

AEGL-3 Values for Automotive Gasoline				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
ND	ND	ND	ND	ND

ND = not determined. AEGL-3 values were not determined due to insufficient data.

GASOLINE
- Summary -

Proposed AEGL Values for Automotive Gasoline					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	1000 mg/m^3	1000 mg/m^3	1000 mg/m^3	1000 mg/m^3	1000 mg/m^3
AEGL-2	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *
AEGL-3	ND	ND	ND	ND	ND

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.
ND = Not determined.

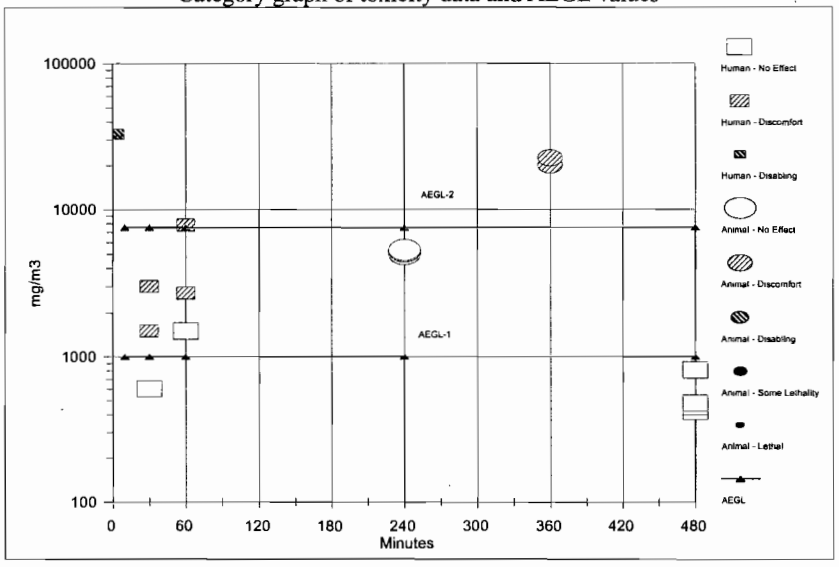
AEGL-1: Exposure of human subjects to 3000 mg/m^3 resulted in slight to intermediate eye irritation. For irritants with an irritation mode of action, an intraspecies uncertainty factor of 3 is sufficient. The same value was used across all exposure durations because there is adaptation to the slight irritation that defines the AEGL-1.

AEGL-2: Exposure of male and female rats to 22,500 mg/m^3 for 6 hours/day was without a significant toxicological effect. Intraspecies and intraspecies uncertainty factors of 1 and 3 were applied. No time scaling.

AEGL-3: AEGL-3 values were *not determined* because studies that addressed the threshold or lethality were not available.

GASOLINE

Category graph of toxicity data and AEGL values



GASOLINE

Data for Derivation of AEGL-2

Key Study: MacFarland et al. 1984
Gasoline was completely volatilized (molecular weight 108)
Both rats and mice were exposed, 6 hours/day. 5 day/week for 103-113 weeks
Concentrations of 67, 292, and 2056 ppm (295, 1290, 9080 mg/m^3)

Point of departure: NOAEL for any relevant human toxic effects in a chronic study

Uncertainty factors??
Interspecies: 1, higher blood:air partition coefficients in rodents for many hydrocarbons
Intraspecies: 1 or 3, the minimum alveolar concentration for narcosis due to solvent inhalation differs approximately 3-fold among individuals.

Time-scaling: none, but could be applied

AEGL-2 Values for Automotive Gasoline				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3000 mg/m^3 9100 mg/m^3 *	3000 mg/m^3 9100 mg/m^3 *	3000 mg/m^3 9100 mg/m^3 *	3000 mg/m^3 9100 mg/m^3 *	3000 mg/m^3 9100 mg/m^3 *

ACUTE EXPOSURE GUIDELINE LEVELS FOR CADMIUM (CAS Reg. No. 7440-43-9)

ORNL Staff Scientist: Jennifer Rayner

Chemical Manager: Susan Ripple

Chemical Reviewers: George Woodall, Marcel van Raaij

Cadmium

- **Conversion**
  - 1 ppm= 4.6 mg/m3
  - 1 mg/m3= 0.22 ppm
- **Physical Characteristics**:
  - Solid-silver-white, blue-tinged lustrous metal
- **Uses**:
  - Consumer and industrial materials
  - Nickel-cadmium batteries, electroplating
  - Pigments in plastics, ceramics, glasses

Human Exposure

- Inhalation of cadmium containing particles, cigarette smoke, fumes/dust in occupational setting
- Fumes/Dust – cough, respiratory irritation, dyspnea, fatigue, nausea, pulmonary edema, pulmonary fibrosis, renal damage, death
- Beton et al. (1966)-Estimated 8.6 mg/m^3 for 5 hours caused pulmonary edema in 5 workers and death in 1 worker (severe pulmonary edema, alveolar metaplasia of the lungs and bilateral cortical necrosis of the kidneys)

Acute Animal Exposure

- Exposure Time: 1-6 hours
- Species: Rabbit, rat
- $CdCl_2$, CdO, CdS, dust, fumes, pigments
- Concentrations:0.07-112 mg/m^3
- Effects: Glutathione activity changes, inflammatory cell influx, pneumonitis, increased lung weight

Repeat Dose Animal Exposure

- Exposure Time: 2 wk-20 wk
- Species: Rat, mouse
- $CdCl_2$, CdO aerosol
- Concentrations:0.025-10 mg/m^3
- Effects: Inflammatory cell influx, pulmonary fibrosis, increased lung weight, renal tubule swelling, epithelium degeneration and necrosis, ataxia, mortality

Uncertainty Factors

- **Interspecies 3, Intraspecies 3-**For acute exposures-direct acting irritant (inflammatory cell influx, pneumonitis, respiratory irritation)
- Chronic exposures-
  - Systemic effects
  - Other factors-diet, age, sex, health status, genetic background
- Time Scale: $C^n \times t = k$, where n = 3 or 1

AEGL-1 Values for Cadmium

- Species: Rat
- Concentration: 0.55 mg Cd/m^3
- Time: 6 hours
- Endpoint: Enzyme changes, no other effect
- Reference: Takenaka et al. 2004
- Support: Single dose at 0.45 mg/m^3 for 2 hours caused increased lung weight and pneumonitis in rats (Grose et al. 1987)

AEGL-1 Values for Cadmium

(mg/m^3)

10-minute	30-minute	1-hour	4-hours	8-hours
0.13	0.13	0.10	0.063	0.041

AEGL-2 Values for Cadmium

- Species: Rat
- Concentration: 5.3 mg Cd/m^3
- Time: 3 hours
- Endpoint: Delayed weight gain, increased- lung weight, protein content, DNA content, cuboidal alveolar cells, inflammatory cells, and focal areas of interstitial thickening
- Reference: Buckley and Bassett 1987
- Support: Single dose at 4.5 mg/m^3 caused pneumonitis, increased lung weight (Grose et al. 1987)

AEGL-2 Values for Cadmium
(mg/m^3)

10-minute	30-minute	1-hour	4-hours	8-hours
1.4	0.96	0.76	0.40	0.20

AEGL-3 Values for Cadmium

- Species: Rat
- Concentration: LC_{50} 112 mg Cd/m^3
- Time: 2 hours
- Endpoint: Threshold of lethality (37.33 mg Cd/m^3)
- Reference: Rusch et al. 1986

AEGL-3 Values for Cadmium
(mg/m^3)

10-minute	30-minute	1-hour	4-hours	8-hours
8.5	5.9	4.7	1.9	0.93

AEGL Values for Cadmium
(mg/m^3)

Classification	Exposure Duration				
	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1 (Notable Discomfort)	0.13	0.13	0.10	0.063	0.041
AEGL-2 (Disabling)	1.4	0.96	0.76	0.40	0.20
AEGL-3 (Lethal)	8.5	5.9	4.7	1.9	0.93

AEGL-1 Takenaka et al. 2004, 0.55 mg Cd/m3 for 6 hours
AEGL-2 Buckley and Bassett 1987 5.3 mg Cd/m3 3 hr
AEGL-3 Rusch et al 1986 2 hr LC50, threshold of lethality

Extant Standards and Guidelines for Cadmium					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 hr**	**4 hr**	**8 hr**
AEGL-1	0.13	0.13	0.10	0.063	0.041
AEGL-2	1.4	0.96	0.76	0.40	0.20
AEGL-3	8.5	5.9	4.7	1.9	0.93
PEL-TWA (OSHA)[a] (fume)					0.1 mg/m^3 0.3 mg/m^{3C}
PEL-TWA (OSHA)[b] (dust)					0.2 mg/m^3 0.6 mg/m^{3C}
IDLH (NIOSH)[c]	9 mg/m^3				
TLV-TWA (ACGIH)[d]					0.01 mg/m^{3I} 0.002 mg/m^{3R}
MAC-Peak Category (The Netherlands)[e]					0.005 mg/m^3

ATTACHMENT 16

AEGLs for RED PHOSPHORUS
(CAS Reg. No. 7723-14-0)

NAC/AEGL Meeting 49
Research Triangle Park, NC
September 9-11, 2009

RED PHOSPHORUS

- **an allotropic form of phosphorus**
- **red phosphorus reacts very slowly with water vapor and air to form phosphine and various phosphorus oxyacids**
- **used as a military obscurant/screen – red phosphorus/butyl rubber (RP/BR) smoke**
  - **military smokes contain ~5% butyl rubber, ~1.25% insulating oil, ~1% talc or silica**
- **other uses include manufacturing of pyrotechnics, safety matches, and fertilizers.**

Summary of Lethal Toxicity of Red Phosphorus or Red Phosphorus/Butyl Rubber Smoke in Animals			
Species	Exposure	Effects (lethality)	Reference
Rat	Ct of 67685-451680 mg/m^3;60-240 min[a]	NOAEL: 1128 mg/m^3; 60 min LOAEL: 1537 mg/m^3; 60 min (10% lethality)	Weimer et al., 1977
	2720-6420 mg/m^3 1 hr[a]	NOAEL: not identified LOAEL : 2720 mg/m^3; 1 hr (20% lethality) LC_{50}: 4597 mg/m^3	Ballou, 1981; Burton et al., 1982
	1210 mg/m^3; 4 hrs[a]	20% lethality	Ballou, 1981; Burton et al., 1982
	680 mg/m^3; 30 min[a] 670 mg/m^3; 30 min[a]	20% lethality 80% lethality	Marrs, 1984
	2000-3150 mg/m^3; 1 hr[a]	NOAEL: 2200 mg/m^3; 1 hr LOAEL: 2620 mg/m^3; 1 hr (6% lethality)	Aranyi, 1983
	450-2130 mg/m^3; 1 hr[b]	NOAEL: 450 mg/m^3; 1 hr LOAEL: 870 mg/m^3; 1 hr (20% lethality) LC_{50}: 1217 mg/m^3 (as phosphorus) LC_{50}: 3846 mg/m^3 (as phosphoric acid)	Ballantyne, 1998
Mouse	111-870 mg/m^3; 1 hr[b]	NOAEL: 111 mg/m^3; 1 hr LOAEL: 136 mg/m^3; 1 hr (2% lethality) LC_{50}: 271 mg/m^3 (as phosphorus) LC_{50}: 856 mg/m^3 (as phosphoric acid)	Ballantyne, 1998
Rabbit	450-2130 mg/m^3; 1 hr[b]	NOAEL: - LOAEL: 450 mg/m^3; 1 hr (10% lethality) LC_{50}: 1689 mg/m^3 (as phosphorus) LC_{50}: 5337 mg/m^3 (as phosphoric acid)	Ballantyne, 1998

Summary of Nonlethal Toxicity of Red Phosphorus or Red Phosphorus/Butyl Rubber Smoke in Animals			
Species	Exposure	Effects	Reference
Dog	Ct of 45570—451,680 mg/m^3; 30-240 min[a]	NOAEL: not identified LOAEL:1519 mg/m^3; 30 min.(respiratory distress); 1882 mg/m^3; 240 min.(conjunctivitis)	Weimer et al., 1977
Rat	Ct of 67685-451680 mg/m^3; 60-240 min[a]	NOAEL: not identified LOAEL: 1128 mg/m^3; 60 min (respiratory distress) 1813 mg/m^3; 180 min. (conjunctivitis)	Weimer et al., 1977
	2000-3150 mg/m^3; 1 hr[a]	no deaths; no additional information	Aranyi, 1986
	1000 mg/m^3; 3.5 hrs[a]	compromised alveolar macrophage function	Aranyi et al, 1988
	450-2130 mg/m^3; 1 hr[b]	NOAEL: not identified LOAEL: 450 mg/m^3; 1 hr (laryngeal and tracheal inflammation)	Ballantyne, 1998
Mouse	11-870 mg/m^3; 1 hr[b]	NOAEL: not identified LOAEL: 111 mg/m^3; 1 hr (mild pulmonary congestion)	Ballantyne , 1998
Rabbit	450-2130 mg/m^3; 1 hr[b]	all exposure tested resulted in lethality	Ballantyne , 1998
Guinea pig	120 mg/m^3; 5 min.[a]	no deaths (exposure to 352 mg/m^3 for 10 min. caused 40% lethality)	Weimer et al., 1977
	36 mg/m^3; 1 hr[b]	no deaths; mild to moderate histopathology in larynx, trachea, and lungs; 1-hr exposure to 52 mg/m^3 caused 45% lethality	Ballantyne, 1998

AEGL-3

AEGL-3 values for red phosphorus (mg/m^3)					
Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	85	59	47	12	5.9

Key Study: Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech.17:251-266.

Critical Effect/POD: 1-hr $BMLC_{05}$ of 469 mg/m^3 for rats used as an estimate of the lethality threshold and POD for AEGL-3 derivation.

Time Scaling: $n = 3$ 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).

Uncertainty Factors: Total UF = 10

Interspecies: 3; responses of the dog, rabbit and guinea pig represented extremes; such variability would normally warrant an interspecies uncertainty factor of 10 but would result in AEGL-3 values inconsistent with human data (15-minute exposures to 100-700 mg/m^3 produced ocular and nasal irritation but no lethalities). The interspecies variability is primarily the result of the extreme sensitivity of guinea pigs.

Intraspecies: 3; ; toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics, which justifies an intraspecies uncertainty factor of 3.

Extant Standards and Guidelines for Red Phosphorus (mg/m^3)					
	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	20	14	11	2.8	1.4
AEGL-3	85	59	47	12	5.9
EEGL	40 (15-min)		10	2 (6-hrs)	
PEGL					1.0
SPEGL	4.0 (15-min)		1.0	0.2 (6-hrs)	
PPEGL					0.1

Intraspecies

Bold= Key Studies

Dichlorvos	Species	Concentration	Exposure	Effect	Reference
	Studies-Inhalation (mg/m^3)				
	Human	**1**	**2-7 hr**	**↓PChE up to 50% ; no clinical symptoms**	**Hunter 1970a**
	Human	43.4-52	10 min-4 hr	Upper respiratory irritation; chest tightness, ↓PChE up to 50%-10 min	Hunter 1970b
	Human	0.5	5 hr/nt, 4 nt/wk for 2 wk	No signs of toxicity; plasma ChE activity inhibited by 34%; erythrocyte ChE activity unaffected;	IPCS 1978
	Human	0.7 (avg.)	8 months	↓PChE 60%, ↓RBC ChE 35%; no clinical symptoms	Menz et al. 1974
	Rat	85-250	4 hr	LC_{50} > 198 mg/m^3 based on 13 of 40 died following exposure to 198-250 mg/m^3	MacDonald 1982
	Rat	**1 -15**	**45 min**	**1-5: Pulmonary morphology changes ≥ 10: dyspnea; ↑ salivation; excessive urination and defecation; alveolar degeneration**	**Atis et al. 2002**
	Mouse	218	4 hr	Hind leg paresis; body tremors; lethargy; subdued; splayed gait	MacDonald 1982
	Mouse	30, 55	16 hr	No cholinergic effects	Dean and Thorpe 1972b
	Mouse	**64, 72**	**16 hr**	**Cholinergic effects**	**Dean and Thorpe 1972a**
	Guinea Pig	35, 55, 75	20 min	Miosis; salivation; lacrimation; AChE ↓24.7-46%, BChE ↓48-69%	Taylor et al. (2008)
	Repeat Studies-Inhalation (mg/m^3)				
	Human 2-7 years	0.04-0.21	~16 hr/d for 18-33 days	No PchE or RBC ChE inhibition	Cavagna et al. 1969
	Human 38-64 years	0.1-0.28	~16 hr/d	↓PChE 32-75%, no clinical signs	Cavagna et al. 1969
	Human Labor and	0.095-0.25	Intermittent for at least 5 d	No PChE or RBC ChE inhibition	Cavagna et al. 1969

	postpartum women				
	Human infants	0.05	continuously for 24 hour followed by 18 hours/day for 4 days	No PChE or RBC ChE inhibition	Cavagna et al. 1970
	Studies-Oral (mg/kg)				
	Human 16-62 yr N=107 males	0.1-32	Single oral	RBC ChE ↓15-65%	Hine and Slomka, 1970; Slomka and Hine 1981
	Human 16-75 yr N=108 male and female	6, 12	Single oral capsule	Patients were malnourished and had severe anemia RBC ChE↓25+% of baseline; brief mild headache, no clinical signs	Pena-Chavarria et al. 1969
	Human N=705 male and female	1, 3, 6, 12	Single oral	No clinical signs; ↓PChE and ↓RBC ChE	Cervoni et al. 1969
	Dog	11, 22	Single oral	11:Moderate-severe toxicity 22:Mild-fatal toxicity	Snow and Watson 1973
	Rat	15; 35	Single oral	15:Miosis, muscle twitch in 1 rat 35: 4/9 killed for humane reasons; Clonic convulsions, muscle twitch	Twomey 2002a,b,c
	Reproductive Developmental Studies				
	Rabbit	0.25-6.25	23 hr/d, 7/d wk, GD1-28	Maternal ChE inhibition NOAEL 0.25 Maternal effects NOAEL 1.25 No effects on fetal resorptions, late fetal deaths, litter size	Thorpe et al. 1972
	Rat	0.25-6.25	23 hr/d, 7/d wk, GD1-20	1.25-6.25 : Maternal-PChE ↓33-73%, RBC ↓29-88%, brain ChE ↓28-83% No developmental toxicity observed	Thorpe et al. 1972
	Mouse	1.9, 3.0, 4.6	4 d, mating or 4 d premating-parturition	Maternal-PChE ↓90-94% No cholinergic signs, no developmental effects	Casebolt et al. 1990

	Mouse	30, 55 2.1, 5.8	16 hr/d or 23 hr/d for 4 wk	No effect on reproductive parameters	Dean and Thorpe 1972b
Intraspecies 1	Traverso et al. (1989) conducted a study showing that DDVP is metabolized by an "A"-esterase (DDVP-ase) that is normally distributed in the population and is distinct from the polymorphic paraoxonase based on heat sensitivity and inhibitory effects of Cd^{++}, Hg^{++}, and Ag^{++}. Studies on the therapeutic efficacy of DDVP for the treatment of intestinal parasites included male and female patients ranging in age from 16-75. Some of the patients were severely debilitated and suffering from malnutrition and severe anemia with hemoglobin levels as low at 3.3 g/dL (Cervoni et al., 1969; Pena Chavarria et al. 1969). No clinical symptoms or signs of organophosphorus poisoning were observed in the patients, and no differences in response to treatment were observed in the patients based on sex, age, or health status. Plasma ChE and erythrocyte ChE activities were not inhibited in eight children (2-7 years old) exposed to 0.04-0.21 mg/m^3 DDVP for ~16 hr/d for 18-33 days (Cavagna et al., 1969). No cholinergic signs or effects on ChE activity was observed in newborn infants exposed by inhalation to DDVP at 0.05 mg/m^3 continuously for 24 hours followed by 18 hours/day for 4 days (Cavagna et al., 1970). In view of this evidence, an intraspecies uncertainty factor is not required to account for polymorphism of the DDVP "A"-esterase in the human population or for differences in humans based on age, sex, or health status.				

Dichrotophos	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	480 720 810 (38.2%) 860	1 hr	Not lethal 4/5 killed Not lethal 1/5 killed	Kettering Laboratory 1965
	Rat	**90**	**1 hr** **4 hr**	**LC_{50}** **LC_{50}**	**Sachsse et al. 1974**
	Rat	250 1250 2500	unspecified	Hyperglycemia at 4 hr; sedation at 8 hr Hypothermia at 4 hr; sedation at 8 hr Hypoglycermia, hypothermia at 4 hr; ataxia at 8 hr	U.S. EPA 2005
	Reproductive/Developmental Studies- No Data				
Intraspecies 10	The default intraspecies uncertainty factor of 10 was maintained for dicrotophos AEGL-3 values. The underlying mechanism of organophosphates is inhibition of cholinesterase by phosphorylation of the esteratic site of the enzyme. Cholinesterases in the blood and tissues are known to be instrumental in limiting the amount of organophosphate compounds reaching critical targets such as brain ChE and acetylChE at cholinergic synapses. Genetic polymorphism has been shown for A-esterases (paraoxonase/arylesterase) in blood and liver of humans. Individuals expressing forms with low hydrolyzing activity are considered to be more susceptible to organophosphate anticholinesterase poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase and these individuals may exhibit greater sensitivity to some anticholinesterase compounds. Evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans (summarized in NRC, 2003). In the absence of chemical-specific data showing that dicrotophos would act contrary to other organophosphate cholinesterase inhibitors, an intraspecies uncertainty factor of 10 was retained.				

Fenamiphos	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat male	29-187	1 hr	LC_{50} 110	Kimmerle 1972
	Rat female	29-320	1 hr	LC_{50} 150	Kimmerle 1972
	Rat male	**83-250**	**1 hr**	**LC_{50} 131**	**Thyssen 1979a**
	Rat female	**83-250**	**1 hr**	**LC_{50} 130**	**Thyssen 1979a**
	Rat male	57-155	4 hr	LC_{50} 100	Thyssen 1979a
	Rat female	57-191	4 hr	LC_{50} 100	Thyssen 1979a
	Reproductive/Developmental Studies- All oral studies (mg/kg)				
	Rabbit	0.1-1.0	GD 6-18 Gavage	Not fetotoxic or embryotoxic, No effect on maternal reproductive parameters	Hazleton Raltech 1982
	Rabbit	0.1-2.5	GD 6-18 Gavage	2.5: 25% maternal mortality, ↓weight gain and food consumption, cholinergic effects	Becker 1986; U.S. EPA 1999
	Rat	0.3-3.0	GD 6-15 Gavage	3.0: cholinergic signs observed within 30 min of treatment	Schlueter 1981
	Rat	0.25-3.0	GD 6-15 Gavage	3.0: Tremors, 6 deaths, ↓weight gain and food consumption	Astroff and Young 1998
	Rat	0.15-1.5	3-gen study Diet	1.5: ↓weight gain in F2 males	U.S. EPA 1999
	Rat	0.17-3.2	2-gen study diet	0.73: ↓RBC ChE in 4-day old pups and adults 2.8, 3.2: F1 pup ↓weight gain, F0 and F1 ↓weight gain during lactation, ↓adult plasma and brain cholinesterase	Eigenberg 1991
Intraspecies 10	Individual variability in plasma cholinesterase activity is well documented (NRC 2003). This variability includes age-related differences (neonates are more susceptible than adults), gender differences (females tend to have approximately 10% lower plasma and red blood cell cholinesterase activity), and genetic variations in plasma cholinesterase activity. This genetically determined variability, sometimes resulting in greatly reduced (64% of normal) activity of plasma cholinesterase may impart deficiencies in ability to detoxify organophosphates such as fenamiphos. Additionally, polymorphic variability in A-esterases such as paraoxonase/ arylesterase, may also contribute to individual variability in organophosphate ester detoxification processes (NRC 2003).				

Malathion	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rabbit	6-123 (MMAD = 12μm)	6 hr	123: ↓PChE 38-41%; ↓RBC ChE 38-49% (Dermal and oral exposure)	Weeks et al. 1977
	Rat	**> 5200**	**4 hr**	**LC_{50}**	**U.S. EPA 2000**
	Mice	**6900 (MMAD = 1.5-2.0 μm)**	**5 hr**	**↓PChE 45%, highly variable**	**Berteau et al. 1976**
	Rat adult	5-450 mg/kg	gavage	93.7: $BMDL_{10}$ 10% ↓RBC ChE	U.S. EPA 2006
	Rat (PND11)	5-450 mg/kg	gavage	31% Tremors 13.6:$BMDL_{10}$ (male) 10% ↓RBC ChE	U.S. EPA 2006
	Reproductive/Developmental Studies- No Data				
Intraspecies 10	To account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases.				

Methami-dophos	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	60-319	1 hour	Calculated LC_{50} (males): 377 Calculated LC_{50} (females): 241	Sangha 1983
	Rat	19-173	4 hours	Calculated LC_{50} (males): 63.2 Calculated LC_{50} (females): 76.5	Sangha 1984
	Rat	**11.4-350.3**	**4 hours**	**Calculated LC_{50}: 213**	**Pauluhn 1986**
	Rat	1.4-5.4 33.1	6 hours	No clinical signs Slight tremor following exposure	Pauluhn 1986
	Rat-oral	1-8 mg/kg	Single dose, PND70	6: ED_{50} for tremors	Moser 1999
	Rat-preweanling	1-8 mg/kg	Single dose, PND17	5: ED_{50} for tremors	Moser 1999
	Reproductive/Developmental Studies- All oral studies (mg/kg)				
	Rat	0.15-1.6	2 gen	0.5:Parental and developmental NOAEL	IPCS 2002; HSDB 2004
	Rat	0.1-2.4	2-gen	0.1:Parental and developmental NOAEL 2.4: Reproduction NOAEL	IPCS 2002; HSDB 2004
	Rabbit	0.1-2.5	GD6-15	2.5: ↓ weight gain	PCS 2002; HSDB 2004
	Rat	0.3-3	GD6-17	1: Developmental NOAEL	PCS 2002; HSDB 2004
	Rat	1-2 mg/kg	GD6-15	1-2: Fetotoxicity	PCS 2002; HSDB 2004
	Mouse	0.4-4 mg/kg	GD16-LD21	Developmental delay	PCS 2002; HSDB 2004
Intraspecies 3	Infants and juveniles may be more sensitive to organophosphate pesticides than adults. An acute oral dosing study with adult and juvenile rats failed to show differences in sensitivity to methamidophos (Moser 1999). Based on repeat-dose oral studies with adult and juvenile rats, the U.S. EPA (2006) identified an FQPA value of 2 to protect children. The FQPA value corresponds to an intraspecies uncertainty factor. Because there were no differences in sensitivity between adult and juvenile rats in the acute oral dosing study, an intraspecies uncertainty factor of 3 is adequate. Although age-related sensitivity is not apparent based on the acute and repeat-exposure oral studies, humans are known to differ in sensitivity to the toxic effects of organophosphate pesticides. There is no data on differences among humans regarding metabolism of methamidophos.					

Methyl Paraoxon Tetraethylpyrophosphate	No Data

Methyl Parathion	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	185 170	4 hr	Male LC_{50} Female LC_{50}	Thyssen 1979
	Rat	34	4 hr	Male LC_{50}	Molnar et al. 1980
	Rat	**108** **134** **168**	**4 hr**	**2 males dead at 98 min.** **3 males dead at 120-129 min.** **5 males, 4 females dead at 43-96 min.**	**U.S. EPA 1998**
	Rat	163 106	4 hr 1.5 hr	100% mortality prior to schedule termination; tremors, salivation, miosis, lacrimation, labored breathing	U.S. EPA 1998
	Rat	200 120	1 hr 4 hr	Male LC_{50} Male LC_{50}	Kimmerle and Lorke 1968
	Rat	257 287	1 hr	Male LC_{50} Female LC_{50}	ATSDR 2001
	Rat	0.9-9.7	6 hr/d, 5 d/wk for 3 wk	9.7: Brain and plasma cholinesterase activity decrease, clinical sings, decreased weight gain	Thyssen and Mohr 1982
	Reproductive/Developmental Studies- No data				
Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.				

Mevinphos	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	12 7.3 9.8	4 hr	Male LC_{50} Female LC_{50} Combined LC_{50}	U.S. EPA 1999
	Rat	9.8	1 hr	LC_{50}	ACGIH 2003
	Rat	**53-346**	**1 hr**	**Female LC_{50} 132**	**Kodama et al. 1954**
	Rat	240	Up to 1 hr	10-15 min- miosis, ear twitching, ↑ chewing 15-40 min- lacrimation, salivation, tremors 40-60 min- respiratory distress, convulsions, death	Kodama et al. 1954
	Reproductive/Developmental Studies- All oral studies (mg/kg)				
	Rabbit	0.05-1.5	GD7-19	0.5:Maternal LOAEL 0.05: Maternal NOAEL 1.5: Developmental NOAEL	U.S. EPA 1999
	Rat	0.20-1.25	GD6-15	0.75: Maternal LOAEL 0.2: Maternal NOAEL 1.0: Developmental NOAEL	U.S. EPA 1999
	Rat	0.05-0.5	2 gen	0.05: Paternal LOAEL Paternal NOAEL not established 0.1: Maternal LOAEL 0.05: Maternal NOAEL 0.5: Developmental LOAEL 0.1: Developmental NOAEL	U.S. EPA 1999
Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.				

Monocrotophos	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	**94** **80**	**1 hr**	**1-hr LC_{50}** **4-hr LC_{50}**	**Sachsse et. al. 1974**
	Rat	63	4 hr	4-hr LC_{50}	ACGIH 2002
	Rat	163 176	1 hr	1-hr LC_{50} 1-hr LC_{50}	Newell and Dilley 1978
	Reproductive/Developmental Studies- No Data				
Intraspecies 10	Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result in greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.				

Parathion	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat male	115 31.5	1 hr 4 hr	LC_{50} LC_{50}	Kimmerle and Lorke 1968
	Rat	30 12	4 hr	LC_{50} Tremors	IUCLID 2000
	Rat male	**31-230.5**	**4 hr**	**84: LC_{50}**	**NIOSH 1974**
	Rat	3-4	2 hr	Lethal to rats	Deichmann et al. 1952
	Rat	134 63	1 hr	Acute cholinergic symptoms Plasma cholinesterase activity inhibition	Pauluhn et al. 1987
	Reproductive/Developmental Studies- No Data				
Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.				

Phorate	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	**11-170**	**1 hr**	**Female LC_{50} = 11** **Male LC_{50} = 60** **Salivation, lacrimation, exophthalmos, defecation, urination, and muscle fasciculations**	**Newell and Dilley 1987**
	Reproductive/Developmental Studies				
	Rat	0.15 0.4 1.94	1 hr/d, GD 7-14	1.94 = Maternal toxicity (50% mortality; all had tremors, lacrimation, and exophthalmos); substantial fetal mortality (31% vs. 7.4% for xylene controls).	Newell and Dilley 1978
Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify using the intraspecies default uncertainty factor of 10.				

Phosphamidon	Species	Concentration (mg/m^3)	Exposure	Effect	Reference
	Adult Studies				
	Rat	160 (nose-only) 180 (nose-only)	1 hour 4 hours	LC_{50} LC_{50}	Sachsse et al. 1974
	Rat	**102 (nose-only) 135 (whole-body)**	**4 hours 4 hours**	**Cholinergic signs LC_{50} LC_{50}**	**Sachsse et al. 1980**
	Mouse	30 <30	1 hour 4 hours	LC_{50} LC_{50}	Sachsse et al. 1974
	Guinea pig	2500 1300	1 hour 4 hours	LC_{50} LC_{50}	Sachsse et al. 1974
	Reproductive/Developmental Studies-Oral Studies				
	Rabbit	1-10 mg/kg	Gavage	10: Maternal toxicity not affecting reproductive or fetal parameters	IPCS 1986; HSDB 2004
	Rat	1-4 mg/kg	Gavage	Maternal toxicity at higher doses resulting in developmental delays and ↓ fetal body weight	IPCS 1986; HSDB 2004
	Rat	5-50 ppm	2 gen, Diet	50: ↓ litter size and survival, tremors, hyperactivity 30: ↓ pup weight, tremors, hyperactivity 5: NOAEL	IPCS 1986; HSDB 2004
	Mice	15 or 35 ppm	Water gestation	35: ↓ implants, litter size, fetal weight, ↑ resorptions	IPCS 1986; HSDB 2004
	Mice	35 ppm	Water 30 or 60 d	30 d: ↓ implants, litter size, fetal weight, ↑ resorptions 60 d: No effects	IPCS 1986; HSDB 2004
Intraspecies 10	There is little information on metabolism differences among humans. The U.S. EPA (U.S. EPA 2006) identified infants and juveniles as populations susceptible to the toxicity of organophosphate pesticides. However, no information was provided for phosphamidon specifically.				

Interspecies

Dichlorvos	0-1.9 mg/m^3	2.0-4.9 mg/m^3	5.0-9.9 mg/m^3	10.0-29.9 mg/m^3	30-49.9 mg/m^3	50-250 mg/m^3	Reference	Relative Potency
Human	1: ↓PChE up to 20%	No effect	No effect	No effect	Upper respiratory irritation-10 min; ↓PChE up to 50%- 4hr	Upper respiratory irritation; chest tightness, ↓PChE up to 50%-10 min	Hunter 1970a,b	0.677: Female brain ChE
Dog	ND	ND	ND	ND	ND	ND		
Rabbit	ND	ND	ND	ND	ND	ND		
Rat	1:Trachea cell cilia loss	2: Trachea cell cilia loss	5:Alveolar interstitial thickening	10-15: alveolar degeneration;↑ cholinergic signs	ND	85-206: cholinergic signs 210:Mortality;	Atis et al 2002; MacDonald 1982	
Mouse	ND	ND	ND	ND	30: No effect	64, 72: OP intoxication	Dean and Thorpe 1972a,b	
Guinea Pig	ND	ND	ND	ND	35: ↓ RChE 24.7% cholinergic signs	55-75:↓ RChE 41-46%, cholinergic signs	Taylor et al 2008	
Oral	**0-5 mg/kg**	**5-10 mg/kg**	**11-15 mg/kg**	**16-20 mg/kg**	**20-25 mg/kg**	**26+ mg/kg**		
Human	1, 3: No effect	6:No effect	12:No effect	ND	22:No effect	32: ↓RChE 65%	Slomka and Hine 1981; Pena-Chavarria et al. 1969; Cervoni et al. 1969	
Dog	ND	ND	11:Moderate-severe toxicity	ND	22:Mild-fatal toxicity	ND	Snow and Watson 1973	
Rat	ND	ND	15:Miosis, muscle twitch in 1 rat	ND	ND	35: 4/9 killed for humane reasons; Clonic	Twomey 2002a,b,c	

						convulsions, muscle twitch		
Human	0.03 mg/kg for 120 days: ↓RChE greater than 10%	0.3 mg/kg for 120 days: ↓RChE greater than 20%	ND	ND	ND	ND	MacGregor 2005	
Rat, Mouse, Dog, Monkey	0.02 mg/kg for 90 days:↓RChE greater than 10%;	0.1 mg/kg for 90 days: ↓RChE greater than 20%	ND	ND	ND	ND	MacGregor 2005	
Interspecies 1	Humans (n=29) exposed once to 1 mg/m^3 or 43.4-52.0 mg/m^3 dichlorvos exhibited 1-50% plasma cholinesterase activity inhibition after 10 minutes to 7 hours (Hunter 1970a,b). Nose and throat irritation was noted by those exposed to 43.4-52.0 mg/m^3. Rats exposed to 1-2 mg/m^3 for 45 minutes experienced shorter trachea epithelial cells and loss of cell cilia (Atis et al. 2002). At 10-15 mg/m^3, clinical signs including dyspnea, increased salivation, excessive urination and defecation were observed. Lethargy, hypersensitivity to noise, body tremors, ataxia, and death were observed in rats exposed to 85-250 mg/m^3 for 4 hours (MacDonald 1982). Guinea pigs exposed to 35-75 mg/m^3 exhibited miosis, salivation, and lacrimation (Taylor et al. 2008). Mice did not exhibit any cholinergic signs after a 16 hour exposure to 30 or 55 mg/m^3 but did after a 16 hour exposure to 64 or 72 mg/m^3 (Dean and Thorpe 1972a,b). Mice exhibited hind leg paresis, body tremors, lethargy, and splayed gait after exposure to 218 mg/m^3 for 4 hours (MacDonald 1982). According to MacGregor et al. (2005), the lowest dose causing greater than 10% inhibition of erythrocyte ChE activity was 0.02 mg/kg at 90 days in animals compared with 0.03 mg/kg in humans at 120 days. The lowest repeat dose causing greater than 20% ChE activity inhibition in animals was 0.1 mg/kg and the next lowest dose was 0.19 mg/kg compared with 0.30 mg/kg as the lowest dose and 1.0 mg/kg, the next lowest in humans. Humans are no more sensitive or possibly less sensitive than laboratory species to dichlorvos.							

Dichrotophos	0-100 mg/m^3	101-500 mg/m^3	501-1000 mg/m^3	1001-1500 mg/m^3	1501-2000 mg/m^3	2001-2500 mg/m^3	Reference	Relative Potency
Human	ND	ND	ND	ND	ND	ND		ND
Dog	ND	ND	ND	ND	ND	ND		
Rabbit	ND	ND	ND	ND	ND	ND		
Rat	90:1 hr LC_{50}, 4 hr LC_{50}	250:Hyperglycemia at 4 hr; sedation at 8 hr	720:80% mortality 860:20% mortality	1250: Hypothermia at 4 hr; sedation at 8 hr	ND	2500: Hypoglycemia, hypothermia at 4 hr; ataxia at 8 hr	Kettering Laboratory 1965; Sachsse et al. 1974, U.S. EPA 2005	
Mouse	ND	ND	ND	ND	ND	ND		
Guinea Pig	ND	ND	ND	ND	ND	ND		
Interspecies 3	Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). The variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.							
Modifying Factor 2	Data deficiencies; data for only one species (rat), conflicting lethality data, and no exposure-response data for nonlethal effects.							

Fenamiphos	**0-15 mg/m^3**	**15-75- mg/m^3**	**75-129 mg/m^3**	**130-175 mg/m^3**	**175+ mg/m^3**	**Reference**	**Relative Potency**
Human	ND	ND	ND	ND	ND		0.315: Female brain ChE
Dog	ND	ND	ND	ND	ND		
Rabbit	ND	ND	ND	ND	ND		
Rat	ND	19+: ↓ChE	110: 1 hr male LC_{50} 100: 4 hr LC_{50}	150: 1 hr female LC_{50} 131: 1 hr male LC_{50} 130: 1 hr female LC_{50}	186+: 90-100% mortality	Kimmerle 1972; Thyssen 1979a	
Mouse	ND	ND	ND	ND	ND		
Guinea Pig	ND	ND	ND	ND	ND		
Interspecies 3	Variability in responses is primarily a function of varying cholinesterase activities and types of cholinesterase. Humans have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as fenamiphos, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase.						

Malathion	0-100 mg/m^3	101-500 mg/m^3	501-1000 mg/m^3	1001-1500 mg/m^3	1501-2000 mg/m^3	2001-2500 mg/m^3	2500+ mg/m^3	Reference
Human	ND	ND	ND	ND	ND	ND	ND	
Dog	67.5:lacrimation, Mild ↓ChE	ND	ND	ND	ND	ND	ND	Hazleton and Holland 1949
Rabbit	ND	123: ↓ChE	810: sneezing	ND	ND	ND	ND	Hazleton and Holland 1949; Weeks et al. 1977
Rat	67.5-moderate ↓ChE 100: LOAEL ↓ChE	ND	ND	ND	ND	ND	>5200: 4-hr LC_{50}	Hazleton and Holland 1949; U.E. EPA 2000
Mouse	ND	ND	ND	ND	ND	ND	6900:↓ChE	Berteau et al. 1976
Guinea Pig	67.5:lacrimation	ND	810: rhinorrhea	ND	ND	ND	ND	Hazleton and Holland 1949
Relative Potency	0.003: Female brain ChE							
Interspecies 3	To account for the differences in serum carboxylesterase levels between humans and rats. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).							
Other information	In humans, hepatic carboxylesterase activities appear similar to those in rat liver. Unlike rats, however, humans lack detectable levels of malathion carboxylesterase activity in the serum; the enzyme is also absent in human erythrocytes. About 30% of blood donors had detectable levels of malathion carboxylesterase activity in serum, activity ranging from 0.1 to 7.2 units/mL; no relation to age, sex, or race was noted. Positive correlations between serum ALT [alanine aminotransferase] and malathion carboxylesterase activities were noted among 46 hospital patients. In addition, activities of the two enzymes in the serum of a patient hospitalized for acetaminophen poisoning were observed to rise and decline in parallel, with the peak being reached on day 4. These data suggest that the low level of malathion carboxylesterase activity found in some human serum is a reflection of liver damage. The lack of malathion carboxylesterase activity in healthy human serum may underlie a significant deviation of pharmacokinetics from the rodent model. [C]linical literature [indicates] that safety of malathion to humans may have been overestimated by acute toxicity data on rats. It has been suggested that rats may not be a proper model and that another species with less extrahepatic carboxylesterase activity may be more appropriate.							

Methami-dophos	0-50 mg/m^3	51-100 mg/m^3	101-150 mg/m^3	151-200 mg/m^3	201-250 mg/m^3	251-300 mg/m^3	301+ mg/m^3	Reference
Human	ND	ND	ND	ND	ND	ND	ND	
Dog	ND	ND	ND	ND	ND	ND	ND	
Rabbit	ND	ND	ND	ND	ND	ND	ND	
Rat	33:10% mortality	56-83:10-80% mortality; 63.2:4-hr male LC_{50} 76.5: 4-hr female LC_{50}	ND	160-196: 30-100% mortality	213:4-hr LC_{50} 241:1-hr LC_{50}	50% mortality	377:1-hr LC_{50}; 350.3: 90% mortality	Sangha 1983, 1984; Pauluhn 1986
Mouse	ND	ND	ND	ND	ND	ND	ND	
Guinea Pig	ND	ND	ND	ND	ND	ND	ND	
Relative Potency	1.000: Female brain ChE							
Interspecies 3	Methamidophos is rapidly metabolized and excreted in rats and humans as indicated by oral dosing studies (Moser 1999; Garofalo et al. 1973).							

Methyl Paraoxon TEEP	No Data								

Methyl parathion	**0-50 mg/m^3**	**51-100 mg/m^3**	**101-150 mg/m^3**	**151-200 mg/m^3**	**201-250 mg/m^3**	**251-300 mg/m^3**	**Reference**	**Relative Potency**
Human	ND	ND	ND	ND	ND	ND		No data
Dog	ND	ND	ND	ND	ND	ND		
Rabbit	ND	ND	ND	ND	ND	ND		
Rat	34:4 hr male LC_{50}	ND	108-134 (4hr): 20-30% mortality 106(1.5 hr): 100% mortality 120:1 hr male LC_{50}	185, 200: 4 hr male LC_{50} 170: 4 hr Female LC_{50} 168 (4hr): 90% mortality 163(4hr):100% mortality	ND	257: 1 hr Male LC_{50} 287:1 hr Female LC_{50}	Thyssen 1979; Molnar et al. 1980; U.S. EPA 1998; Kimmerle and Lorke 1968; ATSDR 2001	
Mouse	ND	ND	ND	ND	ND	ND		
Guinea Pig	ND	ND	ND	ND	ND	ND		
Interspecies 3	Variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as parathion than do other species. This decreases the dose to critical targets.							

Mevinphos	0-50 mg/m^3	51-100 mg/m^3	101-150 mg/m^3	151-200 mg/m^3	201-250 mg/m^3	251+ mg/m^3	Reference	Relative Potency
Human	ND	ND	ND	ND	ND	ND		No data
Dog	ND	ND	ND	ND	ND	ND		
Rabbit	ND	ND	ND	ND	ND	ND		
Rat	12: 4 hr male LC_{50} 7.3: 4 hr female LC_{50} 9.8:1 hr LC_{50}	53-87:17-33% mortality	132: 1 hr female LC_{50}	173:50% mortality	240:10-15 min- mild cholinergic signs 15-40 min- moderate cholingergic signs 40-60 min- respiratory distress, convulsions, death	346:100% mortality	U.S. EPA 1999; ACGIH 2000; Kodama et al. 1954	
Mouse	ND	ND	ND	ND	ND	ND		
Guinea Pig	ND	ND	ND	ND	ND	ND		
Interspecies 3	Variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind antichlolinesterase agents such as mevinphos than do other species.							

Monocrotophos	0-50 mg/m^3	51-100 mg/m^3	101-150 mg/m^3	151-200 mg/m^3	Reference	Relative Potency			
Human	ND	ND	ND	ND		No data			
Dog	ND	ND	ND	ND					
Rabbit	ND	ND	ND	ND					
Rat	ND	4-hr LC_{50}: 63 1-hr LC_{50}: 94 4-hr LC_{50}: 80	ND	1-hr LC_{50}: 163 1-hr LC_{50}: 176	Sachsse et. al. 1974; ACGIH, 2002; Newell and Dilley, 1978				
Mouse	ND	ND	ND	ND					
Guinea Pig	ND	ND	ND	ND					
Interspecies 3	Chemical-specific data with which to assess species variability in the toxicity of inhaled monocrotophos are unavailable (data are limited to rats). The variability in the toxicity of monocrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.								
Modifying Factor 2	Data deficiencies; free-standing LC_{50} values for only one species (rat)								

Parathion	0-50 mg/m^3	51-100 mg/m^3	101-150 mg/m^3	151-200 mg/m^3	Reference	Relative Potency		
Human	ND	ND	ND	ND		No data		
Dog	ND	ND	ND	ND				
Rabbit	ND	ND	ND	ND				
Rat	4-hr LC_{50}: 31.5 4-hr LC_{50}: 30 Tremors: 12	↓PChE: 63 4-hr LC_{50}: 84	1-hr LC_{50}: 115 Cholinergic symptoms: 134	ND	NIOSH 1974; Kimmerle and Lorke 1968; IUCLID 2000; Deichmann et al. 1952; Pauluhn et al. 1987			
Mouse	ND	ND	ND	ND				
Guinea Pig	ND	ND	ND	ND				
Interspecies 3	The mechanism of action of organophosphate anticholinesterases is well understood and their effect on cholinergic systems is consistent across species.							

Phorate	0-10 mg/m^3	11-20 mg/m^3	21-50 mg/m^3	51-100 mg/m^3	101-200 mg/m^3	Reference	Relative Potency		
Human	ND	ND	ND	ND	ND		No data		
Dog	ND	ND	ND	ND	ND				
Rabbit	ND	ND	ND	ND	ND				
Rat	50% Maternal mortality, fetal mortality:1.94	Female LC_{50}: 11		Male LC_{50}: 60		Newell and Dilley 1987			
Mouse	ND	ND	ND	ND	ND				
Guinea Pig	ND	ND	ND	ND	ND				
Interspecies 3	The mechanism of action of organophosphate anticholinesterases is well understood and their action on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase. Humans have been shown to have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds. This decreases the availability of the compound to critical targets (e.g., brain cholinesterase). Therefore, the interspecies uncertainty is limited to 3 as opposed to the default value of 10.								

Phosamidon	0-100 mg/m^3	101-500 mg/m^3	501-1000 mg/m^3	1001-1500 mg/m^3	1501-2000 mg/m^3	2001-2500 mg/m^3	2501+ mg/m^3	Reference
Human								
Dog	ND	ND	ND	ND	ND	ND	ND	
Rabbit	ND	ND	ND	ND	ND	ND	ND	
Rat	ND	1-hr LC_{50}: 160 4-hr LC_{50}: 180 4-hr LC_{50}: 102 (nose-only) 4-hr LC_{50}: 135 (whole-body)	ND	ND	ND	ND	ND	Sachsse et al. 1974, 1980
Mouse	1-hr LC_{50}: 30 4-hr LC_{50}: >30	ND	ND	ND	ND	ND	ND	Sachsse et al. 1974
Guinea Pig	ND	ND	ND	1-hr LC_{50}: 1300	ND	4-hr LC_{50}: 2500	ND	Sachsse et al. 1974
Interspecies 3	Interspecies uncertainty factor of 3 was applied. Rats were more sensitive to the toxicity of phosphamidon than guinea pigs, but not as sensitive as mice. The increased sensitivity of the mouse compared with the rat in the inhalation study of Sachssee et al. (1974) may be related to the higher respiratory rate of mice compared with rats and to the higher levels of glutathione-S-transferase found in mouse tissues (Griem et al. 2002).							
Modifying Factor 2	Sparse data base and conflicting values reported for 1 and 4-hour exposures.							
Metabolism	Metabolism of phosphamidon may also involve conjugation with glutathione. Addition of phosphamidon to human erythrocytes *in vitro* depressed glutathione reductase and glucose-6-phosphate dehydrogenase and increased the level of reduced glutathione, glutathione peroxidase, glutathione-S-transferase, superoxide dismutase, and catalase (Datta et al. 1992). In human plasma, glutathione reductase, glutathione peroxidase, glutathione-S-transferase, glucose-6-phosphate dehydrogenase, superoxide dismutase and levels of reduced glutathione were significantly depressed. Significant depletion of brain glutathione-S-transferase activity was observed following injection of mice with phosphamidon at 2.0 mg/kg/day for seven days (Naqvi and Hasan 1991)							

Chemical	Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
Dichlorvos	AEGL-1	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	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 without an AEGL-2 effect, 5 mg/m^3 (Atis et al. 2002)
	AEGL-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	8.0 ppm 72 mg/m^3	Highest experimental exposure without a lethal effect, 72 mg/m^3 (Dean and Thorpe 1972a)
	Interspecies 1	No mechanistic differences in dichlorvos poisoning in animals and humans. Humans are no more sensitive and possibly less sensitive than laboratory species to DDVP.					
	Intraspecies 1	Documented lack of variability in sensitivity among different age and health groups and genders, and the absence of genetic polymorphisms in DDVP-ase in the population.					
Dicrotophos	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to insufficient data.
	AEGL-2	0.17 mg/m^3	0.17 mg/m^3	0.17 mg/m^3	0.17 mg/m^3	0.083 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001)
	AEGL-3	0.50 mg/m^3	0.50 mg/m^3	0.50 mg/m^3	0.50 mg/m^3	0.25 mg/m^3	Lethality threshold estimated as 3-fold reduction of 1-hr and 4-hr LC_{50} values (90 mg/m^3) in rats (Sachsse et al., 1974)
	Interspecies 3	Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). The variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE activity in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.					
	Intraspecies 10	Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.					
	Modifying Factor 2	limited and conflicting lethality data; limited data regarding non-lethal effects					

Chemical	Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
Fenamiphos	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to exceeding AEGL-2 values
	AEGL-2	0.080 ppm (0.99 mg/m^3)	0.063 ppm (0.78 mg/m^3)	0.053 ppm (0.66 mg/m^3)	0.040 ppm (0.50 mg/m^3)	0.037 ppm (0.46 mg/m^3)	Derived by 3-fold reduction of the AEGL-3 values (NRC 2001; Thyssen 1979a)
	AEGL-3	0.24 ppm (3.0 mg/m^3)	0.19 ppm (2.4 mg/m^3)	0.16 ppm (2.0 mg/m^3)	0.12 ppm (1.5 mg/m^3)	0.11 ppm (1.4 mg/m^3)	Derived based upon a 4-hr $BMCL_{05}$ of 3.7 ppm in rats (Thyssen 1979a)
	Interspecies 3	Variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind antichlolinesterase agents such as fenamiphos than do other species.					
	Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.					
Malathion	AEGL-1	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	Sporadic clinical signs in rats (US EPA 2000)
	AEGL-2	150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3	Clinical signs in rats (US EPA 2000)
	AEGL-3	500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3	Highest experimental concentration (Berteau et al. 1976)
	Interspecies 3	To account for differences in carboxylesterase levels between humans and rats.					
	Intraspecies 10	to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).					
Methyl Parathion	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
	AEGL-2	2.1 mg/m^3	1.5 mg/m^3	1.2 mg/m^3	0.73 mg/m^3	0.37 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; U.S. EPA, 1998)
	AEGL-3	6.4 mg/m^3	4.4 mg/m^3	3.5 mg/m^3	2.2 mg/m^3	1.1 mg/m^3	Derived based upon a 4-hr $BMCL_{05}$ of 66.6 mg/m^3 for lethality in rats (U.S. EPA, 1998)
	Interspecies 3	variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as parathion than do other species. This decreases the dose to critical targets. Therefore, the interspecies uncertainty factor is limited to 3.					
	Intraspecies 10	the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.					

Chemical	Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
Methamidophos	AEGL-1	1.1 mg/m^3	1.1 mg/m^3	0.90 mg/m^3	0.57 mg/m^3	0.29 mg/m^3	No clinical signs – rat (Pauluhn 1986)
	AEGL-2	2.4 mg/m^3	2.4 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	0.61 mg/m^3	No clinical signs –rat (Pauluhn 1986)*
	AEGL-3	5.6 mg/m^3	5.6 mg/m^3	4.5 mg/m^3	2.8 mg/m^3	1.4 mg/m^3	4-hour $BMCL_{05}$ – rat (Pauluhn 1986)
	Interspecies 3	Based on rapid metabolism in both rats and humans (Moser 1999; Garofalo et al. 1973)					
	Intraspecies 10	Based on no differences in sensitivity to acetylcholinesterase activity inhibition between juvenile and adult rats (Moser 1999).					
	Modifying Factor 2	Conflicting data					
Monocrotophos	AEGL-1	NR	NR	NR	NR	NR	Not recommended; insufficient data
	AEGL-2	0.32	0.22	0.17	0.15	0.073	AEGL-2 values estimated by a one-third reduction of AEGL-3 values
	AEGL-3	0.95	0.66	0.52	0.45	0.22	lethality threshold estimated as a 3-fold reduction of 1-hour and 4-hour rat LC_{50} values of 94 mg/m^3 and 80 mg/m^3 (31.3 and 26.7 mg/m^3 respectively) (Sachsse et al., 1974);
	Interspecies 3	Chemical-specific data with which to assess species variability in the toxicity of inhaled dicrotophos are unavailable (data are limited to rats). The variability in the toxicity of dicrotophos and other organophosphate cholinesterase inhibitors is, in part, dependent upon the interaction with other less critical targets such as plasma ChE, carboxylesterases, and red blood cell ChE. In this respect, these cholinesterases may function as an effective repository for organophosphate ChE inhibitors and serve as a buffer against cholinergic-mediated adverse effects. Plasma ChE activity in humans is twice that of mice and four times that of rats. Human plasma ChE also accounts for a greater portion of blood ChE relative to animal species; specifically, approximately 50% of total blood ChE activity in humans is in the form of the noncritical plasma ChE. Further, baseline RBC ChE activity is higher in humans relative to animal species which provides an additional protective advantage.					
	Intraspecies 10	Genetic polymorphisms in some individuals result in enzymes with low hydrolyzing activity and greater susceptibility to organophosphate poisoning. About 3% of individuals possess genetically determined low levels of plasma cholinesterase that may result greater sensitivity to anticholinesterase compounds. These contribute to a decreased potential for preventing interaction of cholinesterase inhibitors with critical targets. Additionally, evidence for gender and age-related variability in the toxic response to organophosphates has been reported for humans and animals.					
	Modifying Factor 2	limited and conflicting lethality data; limited data regarding non-lethal effects					

Chemical	Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
Mevinphos	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
	AEGL-2	0.037 ppm (0.34 mg/m^3)	0.026 ppm (0.24 mg/m^3)	0.021 ppm (0.20 mg/m^3)	0.0053 ppm (0.049 mg/m^3)	0.0078 ppm (0.071 mg/m^3)	Derived by 3-fold reduction of the AEGL-3 values (NRC 2001)
	AEGL-3	0.11 ppm (1.0 mg/m^3)	0.079 ppm (0.72 mg/m^3)	0.062 ppm (0.57 mg/m^3)	0.016 ppm (0.15 mg/m^3)	0.0078 ppm (0.072 mg/m^3)	Derived based upon a 1-hr $BMCL_{05}$ of 1.87 ppm for lethality in rats (Kodama et al. 1954)
	Interspecies 3	Variability in the toxic response is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind antichlolinesterase agents such as fenamiphos than do other species.					
	Intraspecies 10	The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justify retention of the intraspecies uncertainty factor of 10.					
Parathion	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
	AEGL-2	2.8 mg/m^3	1.9 mg/m^3	1.5 mg/m^3	0.96 mg/m^3	0.48 mg/m^3	BMC_{01} (28.9 mg/m^3) for tremors in rats exposed for 4 hrs; UF= 3 x 10 (NIOSH, 1974)
	AEGL-3	3.6 mg/m^3	2.5 mg/m^3	2.0 mg/m^3	1.3 mg/m^3	0.63 mg/m^3	BMC_{01} (37.5 mg/m^3) for lethality in rats exposed for 4 hrs (NIOSH, 1974)
	Interspecies 3	variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as parathion than do other species. This decreases the dose to critical targets. Therefore, the interspecies uncertainty factor is limited to 3.					
	Intraspecies 10	the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.					
Phorate	AEGL-1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
	AEGL-2	0.073 mg/m^3	0.050 mg/m^3	0.040 mg/m^3	0.010 mg/m^3	0.0050 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; Newell and Dilley 1978)
	AEGL-3	0.22 mg/m^3	0.15 mg/m^3	0.12 mg/m^3	0.031 mg/m^3	0.015 mg/m^3	Derived based on the 1-hr LC_{50} of 11 mg/m^3 in female rats (Newell and Dilley 1978)
	Interspecies 3	the default value of 10 was considered unnecessary since variability in toxic response to phorate is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases than do other species. This decreases the dose to critical targets.					
	Intraspecies 10	Thee documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies use of the default intraspecies uncertainty factor of 10.					

Chemical	Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
Phosamidon	AEGL-1	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Insufficient data
	AEGL-2	0.50 mg/m^3	0.50 mg/m^3	0.40 mg/m^3	0.25 mg/m^3	0.13 mg/m^3	AEGL-3 values divided by 3
	AEGL-3	1.5 mg/m^3	1.5 mg/m^3	1.2 mg/m^3	0.75 mg/m^3	0.38 mg/m^3	Four hour LC_{50} in the rat divided by 3 (Sachsse et al. 1980)
	Interspecies 3	the rat was intermediate in sensitivity between the mouse and guinea pig					
	Intraspecies 10	based on the absence of data on differences in human metabolism					
	Modifying Factor 2	based on sparse and disparate data					
Dimethyl Phosphite	AEGL-1	NR	NR	NR	NR	NR	Insufficient data
	AEGL-2	120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)	Labored breathing and ptosis in mice (Hazleton, 1962)
	AEGL-3	360 ppm (1600 mg/m^3)	360 ppm (1600 mg/m^3)	290 ppm (1300 mg/m^3)	180 ppm (800 mg/m^3)	120 ppm (540 mg/m^3)	Labored breathing and ptosis in mice. No mortality (Hazleton, 1962)
	Interspecies 3	no clinical signs were noted in rats and guinea pigs exposed to 1575 ppm for 6 hr.					
	Intraspecies 3	DMP is irritating, 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 between species or among individuals.					
	Modifying Factor 3	Sparse data base and nominal concentration point-of-departure (AEGL-2)					
Trimethylphosphite	AEGL-1	11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)	NOEL for clinical signs in rats (Biodynamics, 1979)
	AEGL-2	110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)	Corneal opacities in rats (Biodynamics, 1979)
	AEGL-3	560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)	Estimated 3-hr lethality threshold in mice (Hazleton, 1962)

	Interspecies 1 (AEGL-2)	Although an interspecies UF of 3 might normally be applied because TMP is an irritant, use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991).
	Interspecies 3	Irritating, toxicity is likely caused by a direct chemical effect on the tissue
	Intraspecies 3	Irritating, type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

OP Table LC_{50} Data

OP	Adult Male LC_{50}	Adult Male CEL	Adult Female LC_{50}	Adult Female CEL	Adult Combined LC_{50}	Juvenile data	Adult Oral Data	Juvenile Oral Data	Intra-species	References
Dichlorvos	ND	0.436 (10%)	ND	0.458 (11%)	4-hr: > 198	ND	ND	ND	1	MacDonald 1982
Dicrotophos	ND	ND	ND	ND	1 hr: 90 4 hr: 90	ND	ND	ND	10	Sachsse et al. 1974
Fenamiphos	1 hr: 110, 131 4 hr: 100	0.928 (0%)	1 hr: 130, 151 4 hr: 100	0.984 (0%)	4 hr: 100	ND	ND	ND	10	Kimmerle 1972; Thyssen 1979a
Malathion	ND	115 (3%)	ND	121 (8%)	4 hr: >5200	ND	93.7 mg/kg: $BMDL_{10}$ 10% ↓RBC ChE	13.6 mg/kg:$BMDL_{10}$ (PND11 male) 10% ↓RBC ChE	10	U.S. EPA 2000, 2006
Methamidophos	1 hr: 377 4 hr: 63.2	0.292 (8%)	1 hr: 241 4 hr: 76.5	0.310 (11%)	4 hr: 213	ND	6 mg/kg: ED_{50} for tremors	5 mg/kg: ED_{50} for tremors (PND17)	3	Sangha 1983, 1984; Pauluhn 1986
Methyl Parathion	1 hr: 200 1 hr: 257 4 hr: 185 4 hr: 34 4 hr: 120	ND	1 hr: 287 4 hr: 170	ND	ND	ND	ND	ND	10	Thyssen 1979; Molnar et al. 1980; Kimmerle and Lorke 1968; ATSDR 2001
Mevinphos	4 hr: 12	ND	4 hr: 7.3 1 hr: 132	ND	4 hr: 9.8	ND	ND	ND	10	U.S. EPA 1999; ACGIH 2003; Kodama et al. 1954
Monocrotophos	ND	ND	ND	ND	1 hr: 94	ND	ND	ND	10	Sachsse et.

					1 hr: 163 1 hr: 176 4 hr: 80 4 hr: 63					al. 1974; ACGIH, 2002; Newell and Dilley, 1978
Parathion	1 hr: 115 4 hr: 31.5 4 hr: 84	ND	ND	ND	4 hr: 30	ND	ND	ND	10	NIOSH 1974; Kimmerle and Lorke 1968; IUCLID 2000; Pauluhn et al. 1987
Phorate	1 hr: 60	ND	1 hr: 11	ND	ND	ND	ND	ND	10	Newell and Dilley 1987
Phosphamidon	ND	ND	ND	ND	1 hr: 160 4 hr: 180 4 hr: 102 4 hr: 135 1 hr mouse: 30 4 hr mouse: >30 1 hr gp: 2500 4 hr gp: >1300	ND	ND	ND	10	Sachsse et al. 1974, 1980
Methyl Paraoxon	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
TEPP	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

CEL= (mg/kg/day) Comparative Effect Level=lowest dose where a maximal response [brain cholinesterase inhibition] of 15% (compared to control) occurred
Relative Potency factors for female brain cholinesterase activity
Rat data except where noted
PND= postnatal day
ND= no data
Concentration mg/m^3 except where noted

Species Comparisons- Inhalation Data

OP	Human	Dog	Rabbit	Rat	Mouse	Guinea Pig	Inter-species	References
Dichlorvos	1-52: Respiratory irritation; ↓PchE up to 50%-10 min	ND	ND	4 hr LC_{50} > 198	64-218: OP intoxicatio n	35-75:↓RChE cholinergic signs	1	Hunter 1970a,b; MacDonald 1982; Dean and Thorpe 1972a,b; Taylor et al 2008
Dicrotophos	ND	ND	ND	1 hr LC_{50} 90 4 hr LC_{50} 90	ND	ND	3	Sachsse et al. 1974
Fenamiphos	ND	ND	ND	1 hr male LC_{50} 110, 131 1 hr female LC_{50} 150, 130 4 hr LC_{50} 100	ND	ND	3	Kimmerle 1972; Thyssen 1979a
Malathion	ND	67.5:lacrimation, Mild ↓ChE	123: ↓ChE 810: sneezing	4-hr LC_{50}>5200	6900:↓Ch E	810: rhinorrhea	3	Hazleton and Holland 1949; U.S. EPA 2000, 2006; Berteau et al. 1976; Weeks et al. 1977
Methamidophos	ND	ND	ND	1 hr male LC_{50} 377 4-hr male LC_{50} 63.2 1 hr female LC_{50} 241 4-hr female LC_{50} 76.5 4-hr LC_{50} 213	ND	ND	3	Sangha 1983, 1984; Pauluhn 1986
Methyl Parathion	ND	ND	ND	1 hr male LC_{50} 200 1 hr male LC_{50} 257 4 hr male LC_{50} 185 4 hr male LC_{50}: 34 4 hr male LC_{50} 120 1 hr female LC_{50}: 287 4 hr female LC_{50}170	ND	ND	3	Thyssen 1979; Molnar et al. 1980; Kimmerle and Lorke 1968; ATSDR 2001
Mevinphos	ND	ND	ND	4 hr LC_{50} 9.8 4 hr male LC_{50}: 12 1 hr female LC_{50}: 132 4 hr male LC_{50} 7.3	ND	ND	3	U.S. EPA 1999; ACGIH 2003;

								Kodama et al. 1954
Monocrotophos	ND	ND	ND	1 hr LC_{50} 94 1 hr LC_{50}: 163 1 hr LC_{50} 176 4 hr LC_{50} 80 4 hr LC_{50} 63	ND	ND	3	Sachsse et. al. 1974; ACGIH, 2002; Newell and Dilley, 1978
Parathion	ND	ND	ND	4 hr LC_{50} 30 1 hr male LC_{50} 115 4 hr male LC_{50} 31.5 4 hr male LC_{50} 84	ND	ND	3	NIOSH 1974; Kimmerle and Lorke 1968; IUCLID 2000; Pauluhn et al. 1987
Phorate	ND	ND	ND	1 hr male LC_{50}: 60 1 hr female LC_{50} 11	ND	ND	3	Newell and Dilley 1987
Phosphamidon	ND	ND	ND	1-hr LC_{50}: 160 4-hr LC_{50}: 180 4-hr LC_{50}: 102 (nose-only) 4-hr LC_{50}: 135 (whole-body)	1-hr LC_{50}: 30 4-hr LC_{50}: >30	1-hr LC_{50}: 2500 4-hr LC_{50}: 1300	10	Sachsse et al. 1974, 1980
Methyl Paraoxon	ND	ND	ND	ND	ND	ND	ND	ND
TEPP	ND	ND	ND	ND	ND	ND	ND	ND

ND= no data
Concentration mg/m^3

BMDS 2.1 – ten Berge C×T Model and Batch Processing

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Concentration × Time modeling

- C×T modeling primarily used in the context of acute inhalation exposures
- Both concentration and duration of exposure important for estimating risk
- Haber's Law; C×T = k
  - Motivation for development of C×T models
  - Assumes consistency across chemicals (i.e., linear relationship between concentration and time)

Concentration x Time modeling

- ten Berge equation; $C^n \times T = k$
- Suggested by ten Berge et al. (1986) as alternative to Haber's Law
  - Observed that CT was not a good parameter for predicting response
  - C^nT predicted response very well
- The value of n indicates which variable influences response more:
  - $n > 1$, concentration dependent
  - $n < 1$, time dependent

ten Berge model in BMDS 2.1

- Represents a unique type of model within BMDS
  - Allows more than one explanatory variable to influence response (e.g., dose and time)
- Implementation in BMDS (C language) faithfully recreates original ten Berge program
  - Originally written in Visual Basic

Mathematical formulation in BMDS

- General form:

$$z = b_0 + b_1 f_c(C) + b_2 f_t(T) + b_3 f_x(x) + b_4 r_4(C,T,x) + \ldots$$

- b_0, b_1, ... are model parameters estimated via maximum likelihood methods
- C = concentration, T = time, and x = some other explanatory variable
- $f_i(u)$ = some transformation on explanatory variable: identity, u; logarithmic, ln(u); or reciprocal, 1/u
- $r_j(C,T,x)$ = interactions (products) of the $f_c(C)$, $f_t(T)$, $f_x(X)$ terms
  - The number of product terms cannot exceed the number of explanatory variables divided by 2 (rounded down)
  - Currently, the model allows 5 explanatory variables and 2 product terms

Mathematical formulation in BMDS

- Model formulation of most interest for acute exposure modeling:

$$z = b_0 + b_1 \ln(C) + b_2 \ln(T)$$

- Can be rearranged as:

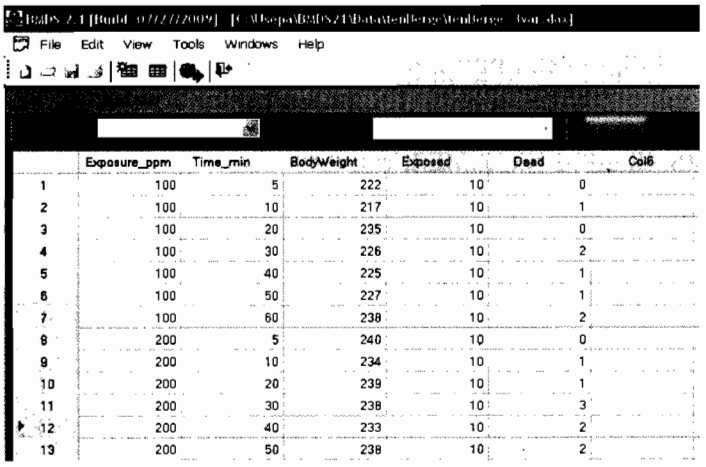
$$z = b_0 + b_2 \ln(C^n \times T)$$

- Where n = b_1 / b_2

Formatting data for ten Berge model

- Data format
  - Can create data sets in excel or other spreadsheet applications and copy/paste into BMDS
  - Data needs to be formatted so data is presented in sequential columns (i.e., column 1 = dose, column 2 = number of subjects, etc.)
- Data set needs at minimum:
  - Total number of subjects
  - Number of affected subjects
  - 2 explanatory variables

Formatting data for ten Berge model



	Exposure_ppm	Time_min	BodyWeight	Exposed	Dead	Col6
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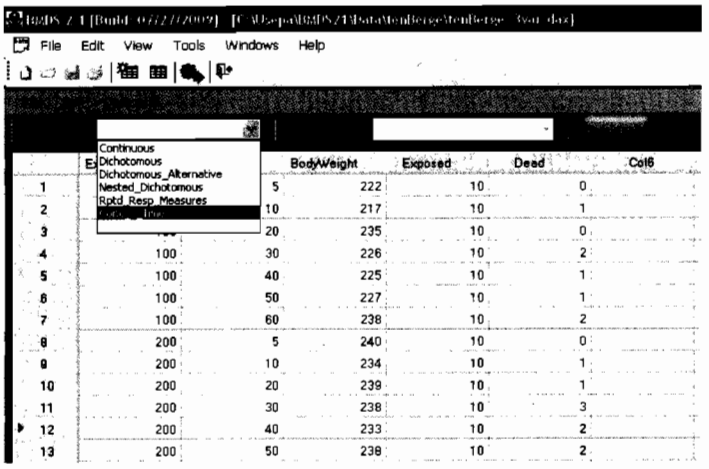
2	100	10	217	10	1	
3	100	20	235	10	0	
4	100	30	226	10	2	
5	100	40	225	10	1	
6	100	50	227	10	1	
7	100	60	238	10	2	
8	200	5	240	10	0	
9	200	10	234	10	1	
10	200	20	239	10	1	
11	200	30	238	10	3	
12	200	40	233	10	2	
13	200	50	238	10	2	

Select "Conc × Time" from Model Type menu



	Exposure_ppm	Time_min	BodyWeight	Exposed	Dead	Col6
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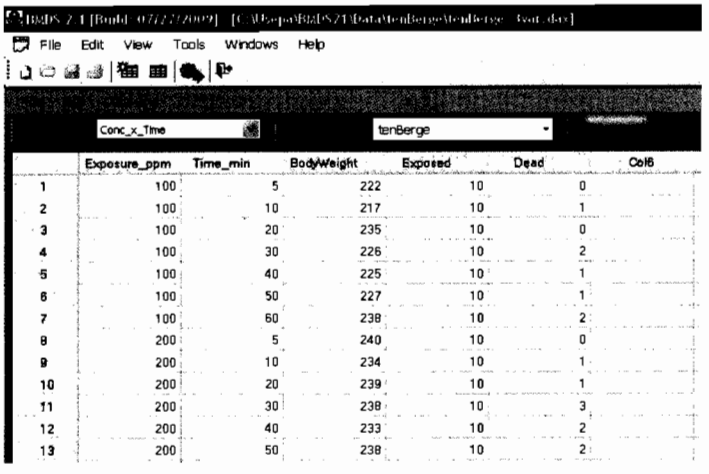
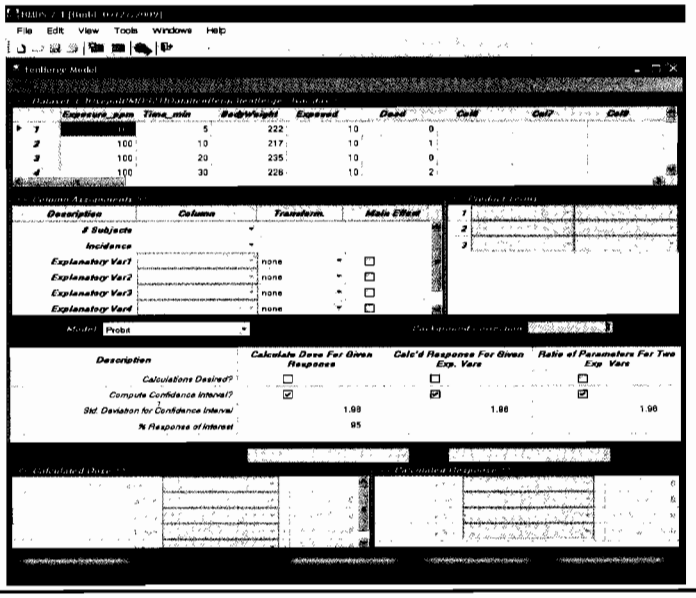
2		10	217	10	1	
3		20	235	10	0	
4	100	30	226	10	2	
5	100	40	225	10	1	
6	100	50	227	10	1	
7	100	60	238	10	2	
8	200	5	240	10	0	
9	200	10	234	10	1	
10	200	20	239	10	1	
11	200	30	238	10	3	
12	200	40	233	10	2	
13	200	50	238	10	2	

ten Berge model is automatically selected



	Exposure_ppm	Time_min	BodyWeight	Exposed	Dead	Col6
1	100	5	222	10	0	
2	100	10	217	10	1	
3	100	20	235	10	0	
4	100	30	226	10	2	
5	100	40	225	10	1	
6	100	50	227	10	1	
7	100	60	238	10	2	
8	200	5	240	10	0	
9	200	10	234	10	1	
10	200	20	239	10	1	
11	200	30	238	10	3	
12	200	40	233	10	2	
13	200	50	238	10	2	

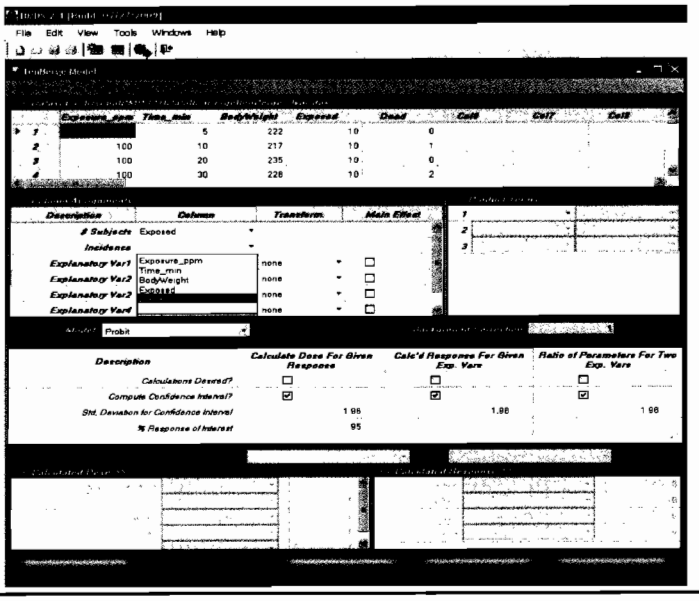
ten Berge model Option Screen



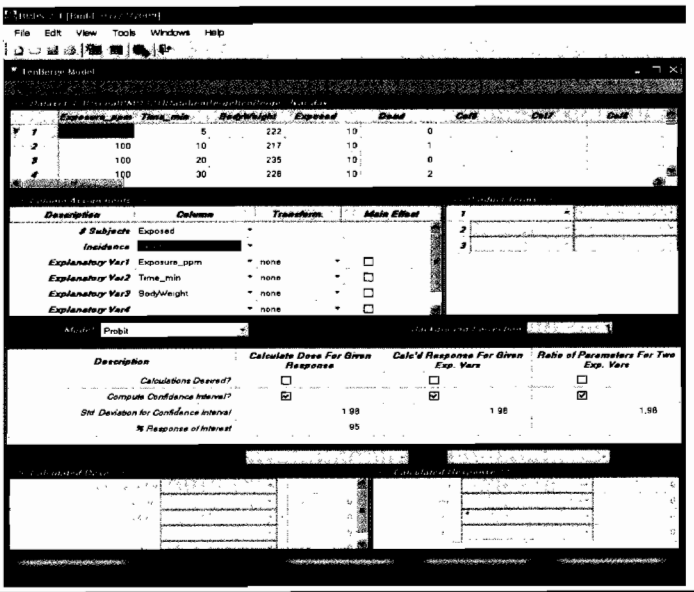
Running the ten Berge model

- To run the model, the user must:
  - Make the appropriate column assignments for: (1) number of subjects, (2) incidence, and (3) explanatory variables
  - Choose transformations to apply to explanatory variables
  - Choose explanatory variables to include as main effects
  - Choose product terms to include
  - Choose model (Probit or Logistic) to use
  - Decide which estimates and confidence intervals the model should estimate (e.g., value for one explanatory variable, give values for the other explanatory variables and probability of response)

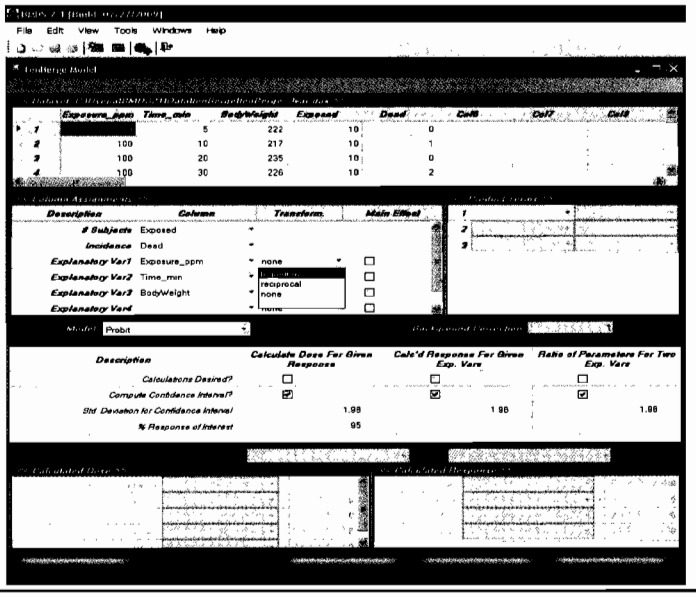
Make appropriate column selections



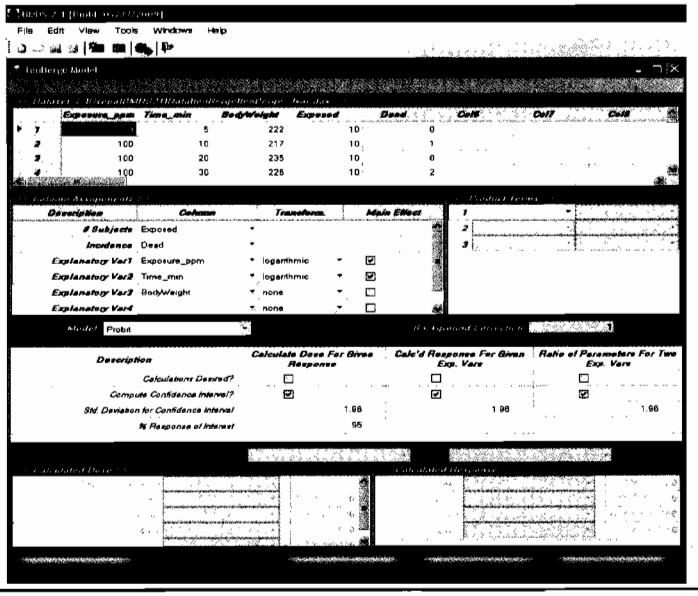
Make appropriate column selections



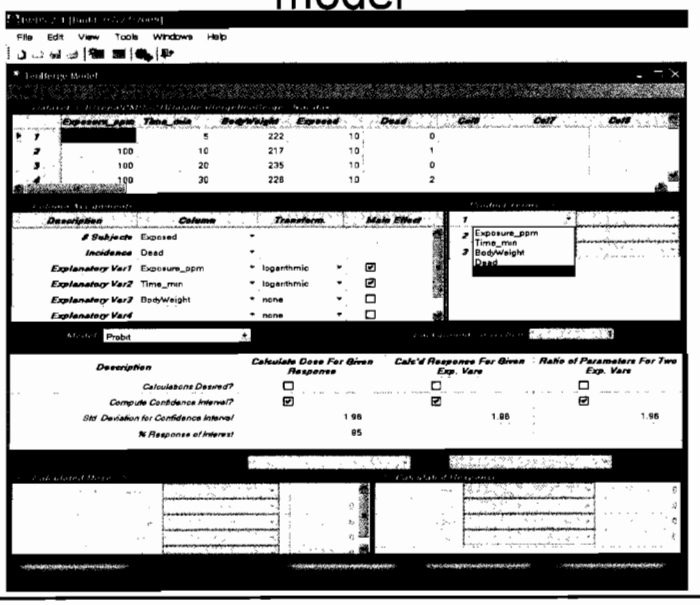
Choose appropriate transformations



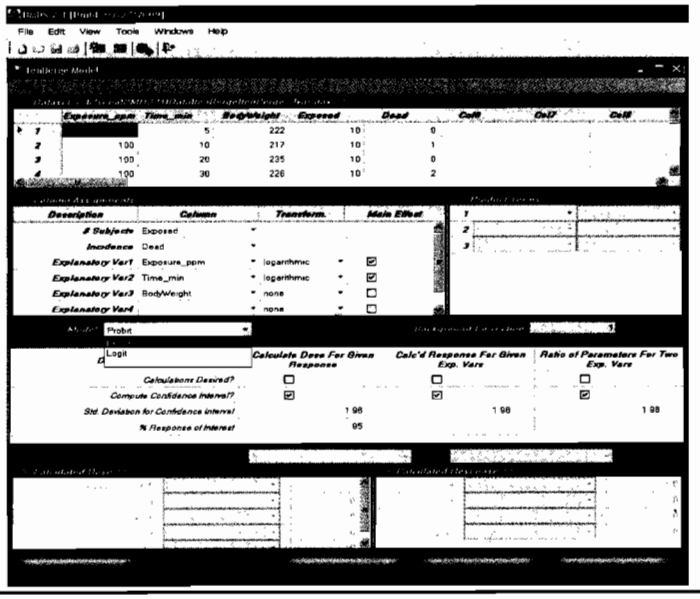
Choose Main Effects to include in model



Choose Product Terms to include in model



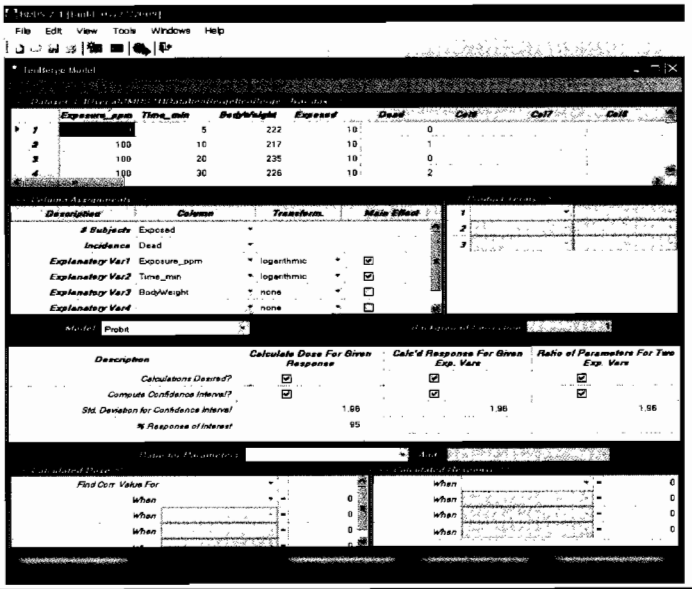
Choose which model to use



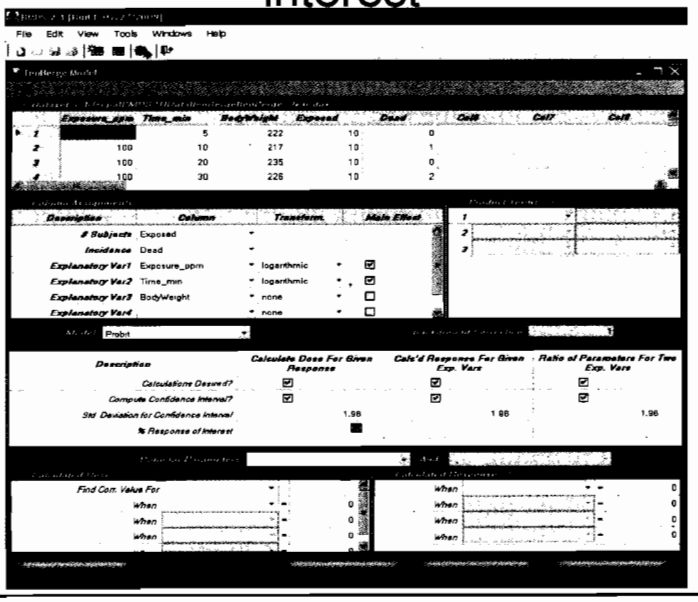
Choose model calculations of interest

- In the Model Option Screen, the user can request estimates and confidence limits for the following:
  - A value of one of the explanatory variables, given the probability of response and specified values for the other explanatory variables
  - The probability of response given specified values for all the explanatory variables
  - The ratio between the coefficients of two explanatory variables

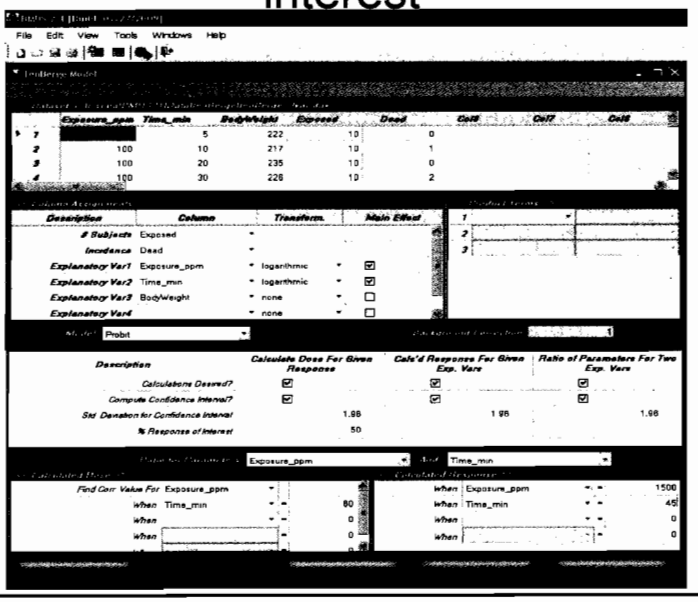
Choose model calculations of interest



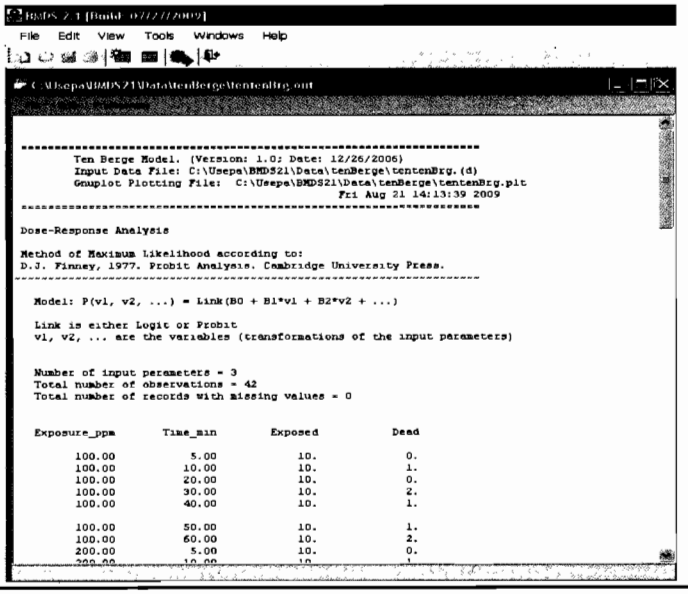
Select model options for calculations of interest



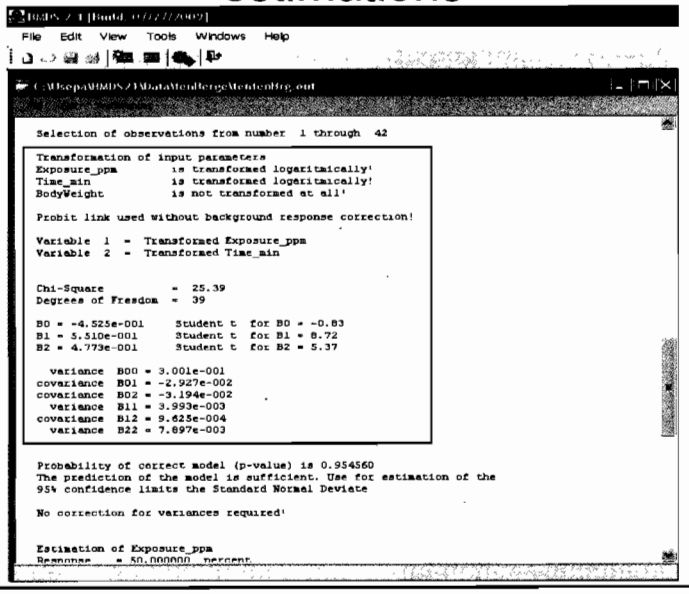
Select model options for calculations of interest



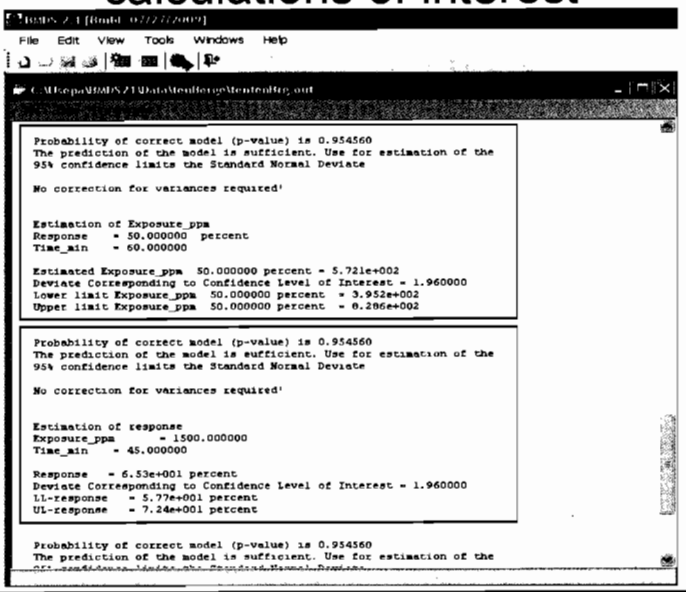
ten Berge model output



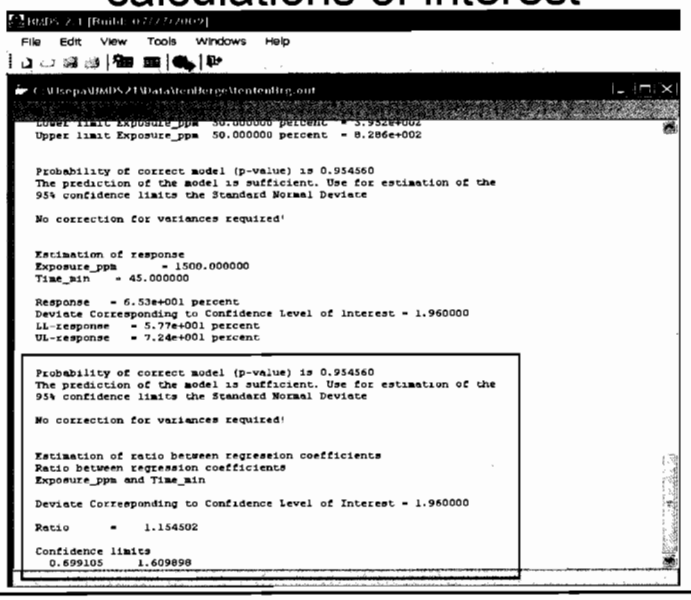
ten Berge model output – parameter estimations



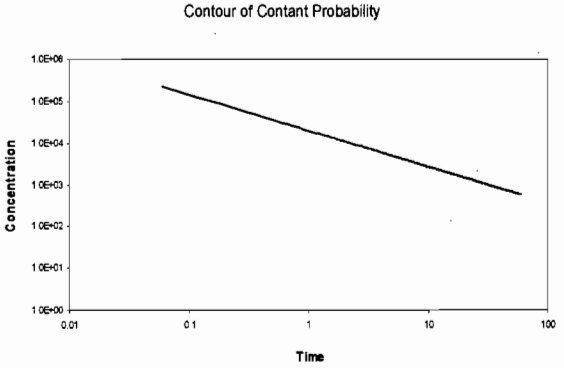
ten Berge model output – results of calculations of interest



ten Berge model output – results of calculations of interest

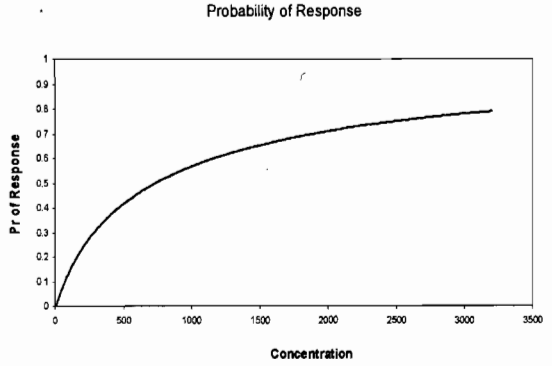


ten Berge plots



- For this example, the contour line represents the logarithm of the dose resulting in 50% mortality (i.e., the LC_{50}) plotted against the logarithm of exposure duration
- $n = 1.15$ ($n = b_1 / b_2 = 0.5510/0.4773$), indicating that exposure concentration influences response to a greater degree than exposure time

ten Berge plots

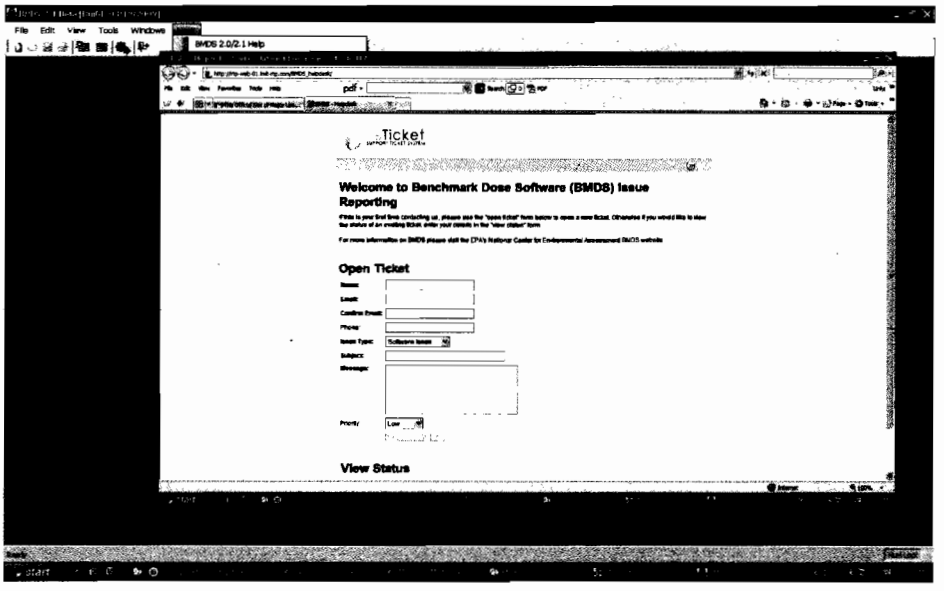


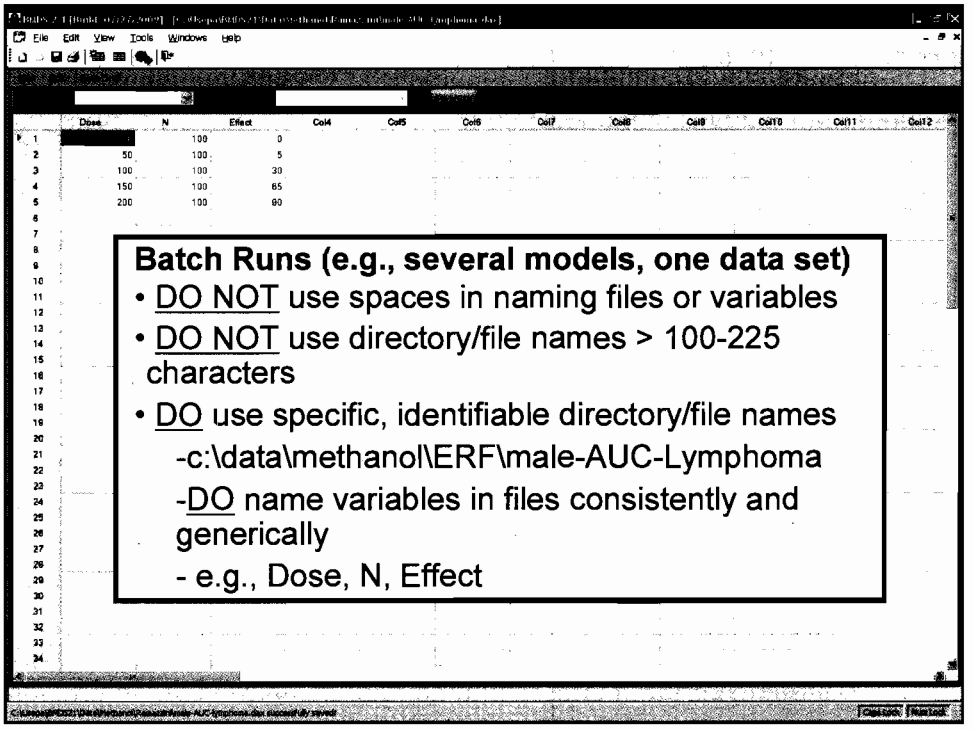
- For this example, the red line represents the probability of response plotted against exposure concentration when exposure time = 45 minutes

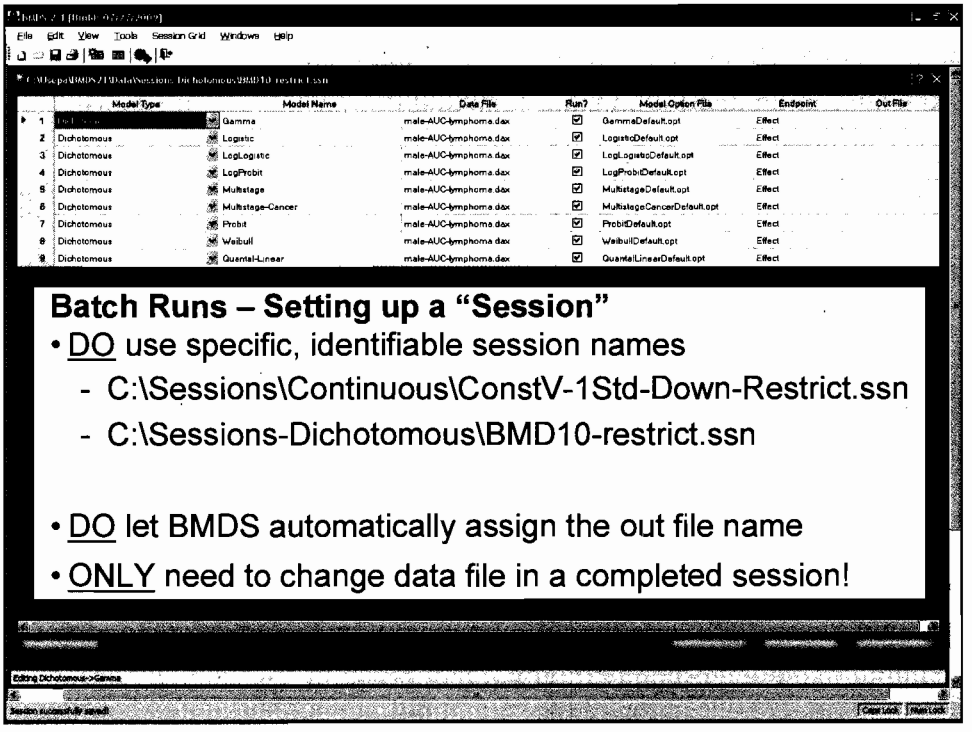
New Features/Models in BMDS 2.1

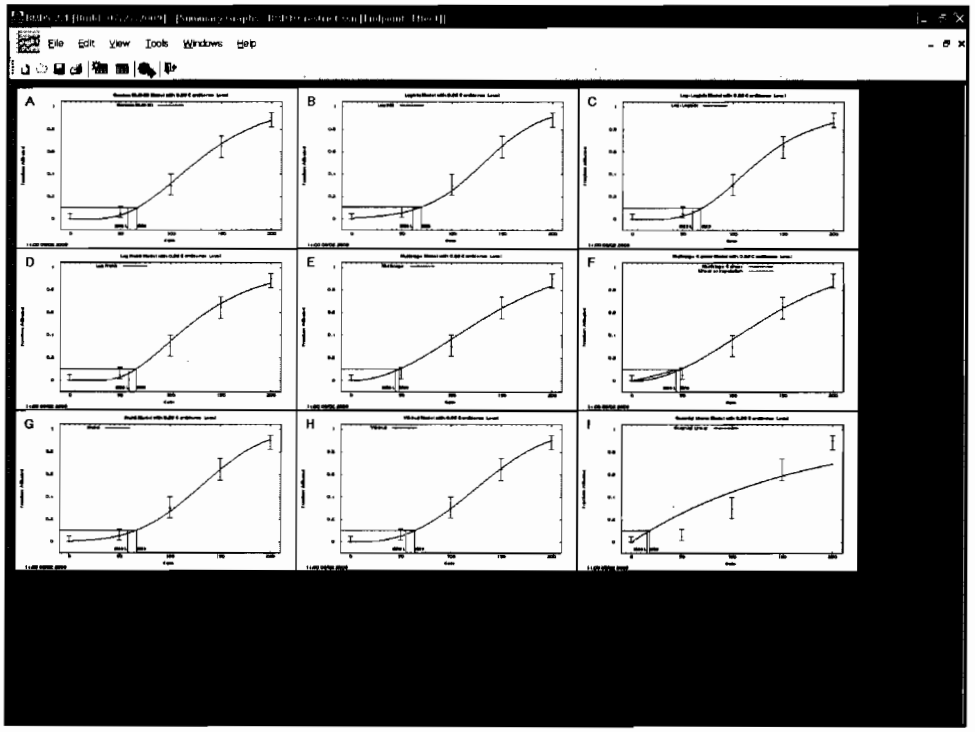
- Interface: New and Enhanced
- New Modeling Capabilities
  - Session feature facilitates batch runs and summary reports
  - Lognormal option (continuous exponential models)
  - Setting background to zero for data with no control group
- Dichotomous Models
  - Dichotomous Hill Model
  - New Background Dose/Response Models
- Continuous Models
  - Exponential Models
- Repeated Response Measures
  - Toxicodiffusion Model (version 2.1)
- Concentration X Time
  - Ten Berge Model
- Problem Reports: New "eTicket" & "Problem Log" features

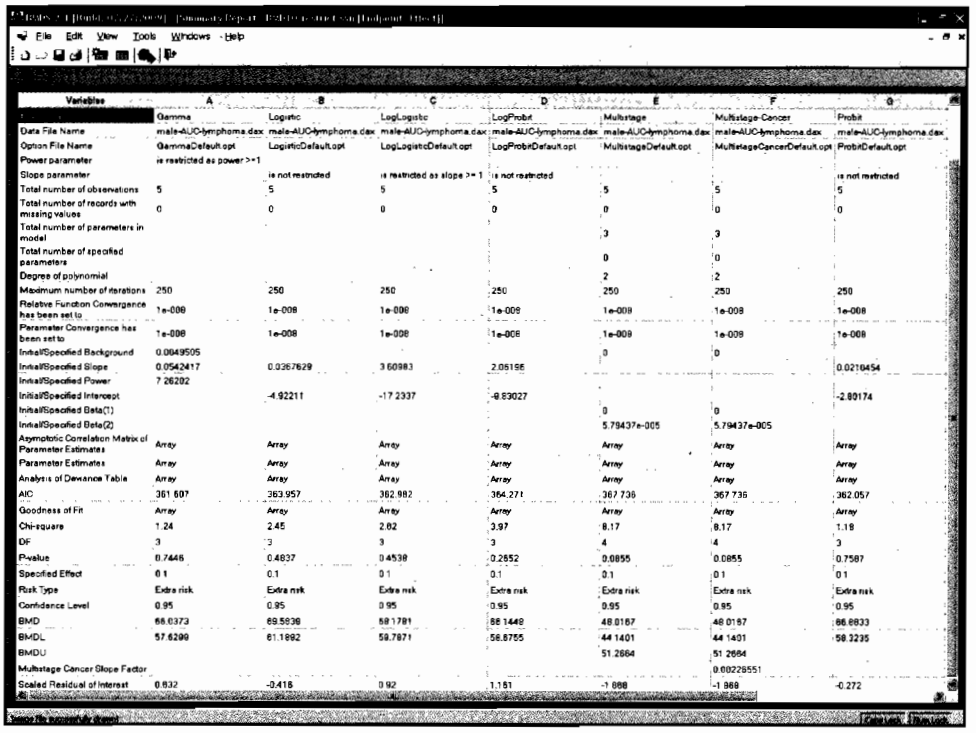
Problem Reporting




File Edit View Tools Windows Help
Dose N Effect Col4 Col5 Col6 Col7 Col8 Col9 Col10 Col11 Col12
1 100 0
2 50 100 5
3 100 100 30
4 150 100 65
5 200 100 90
Batch Runs (e.g., several models, one data set)
• DO NOT use spaces in naming files or variables
• DO NOT use directory/file names > 100-225 characters
• DO use specific, identifiable directory/file names
-c:\data\methanol\ERF\male-AUC-Lymphoma
-DO name variables in files consistently and generically
- e.g., Dose, N, Effect


File Edit View Tools Session Grid Windows Help
Model Type Model Name Data File Run? Model Option File Endpoint Out File
1 Gamma male-AUC-lymphoma.dax GammaDefault.opt Effect
2 Dichotomous Logistic male-AUC-lymphoma.dax LogisticDefault.opt Effect
3 Dichotomous LogLogistic male-AUC-lymphoma.dax LogLogisticDefault.opt Effect
4 Dichotomous LogProbit male-AUC-lymphoma.dax LogProbitDefault.opt Effect
5 Dichotomous Multistage male-AUC-lymphoma.dax MultistageDefault.opt Effect
6 Dichotomous Multistage-Cancer male-AUC-lymphoma.dax MultistageCancerDefault.opt Effect
7 Dichotomous Probit male-AUC-lymphoma.dax ProbitDefault.opt Effect
8 Dichotomous Weibull male-AUC-lymphoma.dax WeibullDefault.opt Effect
9 Dichotomous Quantal-Linear male-AUC-lymphoma.dax QuantalLinearDefault.opt Effect
Batch Runs – Setting up a "Session"
• DO use specific, identifiable session names
- C:\Sessions\Continuous\ConstV-1Std-Down-Restrict.ssn
- C:\Sessions-Dichotomous\BMD10-restrict.ssn
• DO let BMDS automatically assign the out file name
• ONLY need to change data file in a completed session!





Variables	A	B	C	D	E	F	G
	Gamma	Logistic	LogLogistic	LogProbit	Multistage	Multistage-Cancer	Probit
Data File Name	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax	male-AUC-lymphoma.dax
Option File Name	GammaDefault.opt	LogisticDefault.opt	LogLogisticDefault.opt	LogProbitDefault.opt	MultistageDefault.opt	MultistageCancerDefault.opt	ProbitDefault.opt
Power parameter	is restricted as power >=1						
Slope parameter		is not restricted	is restricted as slope >= 1	is not restricted			is not restricted
Total number of observations	5	5	5	5	5	5	5
Total number of records with missing values	0	0	0	0	0	0	0
Total number of parameters in model					3	3	
Total number of specified parameters					0	0	
Degree of polynomial					2	2	
Maximum number of iterations	250	250	250	250	250	250	250
Relative Function Convergence has been set to	1e-008	1e-008	1e-008	1e-008	1e-008	1e-008	1e-008
Parameter Convergence has been set to	1e-008	1e-008	1e-008	1e-008	1e-008	1e-008	1e-008
Initial/Specified Background	0.0049505				0	0	
Initial/Specified Slope	0.0542417	0.0367629	3.60983	2.05195			0.0216454
Initial/Specified Power	7.26202						
Initial/Specified Intercept		-4.92211	-17.2337	-8.83027			-2.80174
Initial/Specified Beta(1)					0	0	
Initial/Specified Beta(2)					5.79437e-005	5.79437e-005	
Asymptotic Correlation Matrix of Parameter Estimates	Array	Array	Array	Array	Array	Array	Array
Parameter Estimates	Array	Array	Array	Array	Array	Array	Array
Analysis of Deviance Table	Array	Array	Array	Array	Array	Array	Array
AIC	361.607	363.957	362.982	364.271	367.736	367.736	362.057
Goodness of Fit	Array	Array	Array	Array	Array	Array	Array
Chi-square	1.24	2.45	2.62	3.97	8.17	8.17	1.18
DF	3	3	3	3	4	4	3
P-value	0.7446	0.4837	0.4538	0.2652	0.0855	0.0855	0.7587
Specified Effect	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Risk Type	Extra risk	Extra risk	Extra risk	Extra risk	Extra risk	Extra risk	Extra risk
Confidence Level	0.95	0.95	0.95	0.95	0.95	0.95	0.95
BMD	66.0373	69.5836	68.1781	68.1449	48.0187	48.0187	66.8833
BMDL	57.6299	61.1892	59.7971	56.8755	44.1401	44.1401	58.3235
BMDU					51.2684	51.2684	
Multistage Cancer Slope Factor						0.00226551	
Scaled Residual of Interest	0.632	-0.418	0.92	1.161	-1.868	-1.868	-0.272

Sample Documentation of BMD Analysis
(Exported from BMDS summary to Excel Spreadsheet)

	Goodness of fit p value	AIC	Scaled Residual	BMD	BMDL
Gamma	0.7446	361.607	0.632	66.04	57.63
Logistic	0.4837	363.957	-0.416	69.58	61.19
LogLogistic	0.4538	362.982	0.920	68.18	59.79
LogProbit	0.2652	364.271	1.161	66.14	58.68
Multistage	0.0855	367.736	-1.868	48.02	44.14
Probit	0.7587	362.057	-0.272	66.88	58.32
Weibull	0.9994	360.400	-0.087	64.24	55.21
Quantal-Linear	0.0000	423.594	0.000	17.68	15.65

Future BMDS Models & Features

- Multitumor model (MS_combo)
- Dichotomous and Continuous model trend test
- Lognormal distribution for more models
- "Hybrid" feature for continuous models
- User defined output summary tables
- Improved export (e.g., Excel) features
- Feature for improving initial parameter estimates
- User-friendly access to more R programs (e.g., CatReg)
- BMD model averaging

Useful Links

- National Center for Environmental Assessment
  - BMDS Main Website – http://www.epa.gov/ncea/bmds/
  - BMDS Training Website - http://www.epa.gov/ncea/bmds/training/index.html
- RIVM Netherlands
  - PROAST software Website - http://www.rivm.nl/en/foodnutritionandwater/foodsafety/proast.jsp

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix A

* APPROVE MINUTES from NAC/AEGL 48 **Chemical:** **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					John Hinz				
Marc Baril					Jim Holler				
Lynn Beasley					Clarion Johnson				
Alan Becker					Glenn Leach				
Robert Benson					Richard Niemeier				
Edward Bernas					Mattias Oberg				
Iris Camacho					Susan Ripple				
George Cushmac					George Rusch, Chair				
Richard Erickson					Daniel Sudakin				
Neeraja Erraguntla					Marcel vanRaaij				
David Freshwater					George Woodall				
Ralph Gingell					Alan Woolf				
					TALLY				
					PASS/ FAIL				

* UNANIMOUS

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Benson **Second by:** Freshwater
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/9/09

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

<u>Selected Cyanide Salts</u>
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 ($C^n \times t = k$) 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 ($C^n \times t = k$) 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

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix C

Chemical: DIMETHYL PHOSPHITE **CAS Reg. No.:** 868-85-9

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: CUSHMAC **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	Y	P	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY	20/20	20/20	20/20	
					PASS/ FAIL	P	P	P	

~~PPM~~, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (NR)	, (NR)	, (NR)	, (NR)	, (NR)
AEGL 2	, (120)	, (120)	, (95)	, (60)	, (39)
AEGL 3	, (190)	, (190)	, (150)	, (96)	, (63)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of Data

AEGL 1 Motion by: RIPPLE **Second by:** HOLLER
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/9/09

NAC/AEGL Meeting 49: September 9-11, 2009

Chemical: TRIMETHYL PHOSPHITE **CAS Reg. No.:** 121-45-9

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: CUSHMAC **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	P	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY	19/19	20/20	20/20	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(11)	,(7.6)	,(6.1)	,(3.8)	,(2.5)
AEGL 2	,(110)	,(77)	,(61)	,(38)	,(25)
AEGL 3	,(560)	,(390)	,(310)	,(160)	,(81)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1 Motion by: Benson **Second by:** Niemeier
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/9/09

NAC/AEGL Meeting 49: September 9-11, 2009

Chemical: METHYL IODIDE **CAS Reg. No.:** 74-88-4

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager:

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y	Y	Y	
Marc Baril	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Alan Becker	Y	Y	Y	
Robert Benson	P	P	P	
Edward Bernas	Y	Y	Y	
Iris Camacho	A	A	A	
George Cushmac	Y	Y	Y	
Richard Erickson	Y	Y	Y	
Neeraja Erraguntla	Y	Y	Y	
David Freshwater	Y	Y	Y	
Ralph Gingell	Y	Y	Y	

Staff Scientist:

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
John Hinz	Y	Y	Y	
Jim Holler	Y	Y	Y	
Clarion Johnson	A	A	A	
Glenn Leach	A	A	A	
Richard Niemeier	Y	Y	Y	
Mattias Oberg	Y	Y	Y	
Susan Ripple	Y	Y	Y	
George Rusch, Chair	Y	Y	X	
Daniel Sudakin	A	A	A	
Marcel vanRaaij	Y	Y	Y	
George Woodall	Y	Y	Y	
Alan Woolf	Y	Y	Y	
TALLY	19/19	19/19	19/19	
PASS/ FAIL	✓	✓	✓	

PPM (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(54)	,(31)	,(22)	,(11)	,(11)
AEGL 2	,(200)	,(120)	,(82)	,(41)	,(29)
AEGL 3	,(670)	400,(390)	,(~~290~~ 280)	,(150 ~~150~~)	,(~~98~~ 86)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

} BT

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: Van Raaij **Second by:** Woodall
AEGL 2 Motion by: / **Second by:** /
AEGL 3 Motion by: / **Second by:** /
LOA Motion by: **Second by:**

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix F

Chemical: PHOSGENE (NEW DATA) **CAS Reg. No.:** 75-44-5 PROPOSED REVISIONS

Action: Proposed_____ **Interim**_____ **Other** REVISION OF FINAL PHOSGENE VALUES BASED ON NEW DATA

Chemical Manager: FALKE **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	P	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(2.3)	,(0.77)	,(0.38)	,(0.096)	,(0.048)
AEGL 3	,(7.8)	,(2.6)	,(1.3)	,(0.33)	,(0.16)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: Benson **Second by:** Baril
AEGL 2 Motion by: _____ **Second by:** _____
AEGL 3 Motion by: _____ **Second by:** _____
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DEO:** _____ **Date:** 9/9/09

Chemical: DICROTOPHOS **CAS Reg. No.:** 141-66-2 Appendix G

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: HINZ **Staff Scientist:** RAYNER

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY				
					PASS/ FAIL				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(8.53 / 1.82)	,(0.37 / 0.42)	,(0.29 / 0.34)	,(0.073 / 0.086)	,(0.037 / 0.042)
AEGL 3	,(1.8 / 1.6)	,(1.3 / 1.1)	,(1.0 / 0.88)	,(0.26 / 0.22)	,(0.1 / 0.13)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of Data

AEGL 1 Motion by: HINZ **Second by:** BARIL
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] DEO, Paul Tobin **Date:** 9/10/09

NAC/AEGL Meeting 49: September 9-11, 2009

Chemical: Monocrotophos **CAS Reg. No.:** 6923-22-4

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: Benson **Staff Scientist:** Young

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY	20/20	20/20	20/20	
					PASS/ FAIL	P	P	P	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(~~0.43~~ 0.44)	,(~~0.31~~ 0.32)	,(0,24)	,(~~0.21~~ 0.22)	,(~~0.19~~ 0.11)
AEGL 3	,(1.3)	,(0,92)	,(~~0.74~~ 0.73)	,(~~0.64~~ 0.62)	,(~~0.32~~ 0.31)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of Data

AEGL 1 Motion by: Hinz **Second by:** Baril
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: **Second by:**

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix I

Chemical: METHAMIDOPHOS **CAS Reg. No.:** 10265-92-6

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: ANDERSON **Staff Scientist:** TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	P	P	P	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	P	P	P	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	P	P	P	
David Freshwater	Y	Y	Y		George Woodall	P	P	P	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY	16/16	16/16	16/16	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(2.4)	,(2.4)	,(1.9)	,(1.2)	,(0.61)
AEGL 2	,(4.5)	,(4.5)	,(3.6)	,(2.3)	,(1.1)
AEGL 3	10,( )	10 ,( )	8.1 ,( )	5.1 ,( )	2.5,( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: Anderson **Second by:** Niemeier
AEGL 2 Motion by: / **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/10/09

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix J

Chemical: * MEVINPHOS **CAS Reg. No.:** 7786-34-7

Action: Proposed ~~P~~ **Interim**_____ **Other** HOLDING

Chemical Manager: ANDERSON **Staff Scientist:** TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	P				John Hinz	Y			
Marc Baril	Y				Jim Holler	Y			
Lynn Beasley	Y				Clarion Johnson	A			
Alan Becker	Y				Glenn Leach	A			
Robert Benson	Y				Richard Niemeier	P			
Edward Bernas	Y				Mattias Oberg	Y			
Iris Camacho	A				Susan Ripple	Y			
George Cushmac	Y				George Rusch, Chair	Y			
Richard Erickson	P				Daniel Sudakin	A			
Neeraja Erraguntla	P				Marcel vanRaaij	Y			
David Freshwater	Y				George Woodall	Y			
Ralph Gingell	Y				Alan Woolf	Y			
					TALLY	16/16			
					PASS/ FAIL	HOLDING			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

* PLACE IN HOLDING CATEGORY DUE TO LACK OF DATA.

NR= Not Recommended due to_____

AEGL 1 Motion by: Woodall **Second by:** Hinz
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/10/09

NAC/AEGL Meeting 49: September 9-11, 2009

Chemical: PHOSPHAMIDON **CAS Reg. No.:** 13171-21-6 Appendix K

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: BERNAS **Staff Scientist:** TALMAGE

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	P	P	P		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	P	P	P	
Edward Bernas	Y	Y	Y		Mattias Oberg	P	P	P	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	N	N	N	
David Freshwater	Y	Y	Y		George Woodall	N	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	N	Y	Y	
					TALLY	16/16	16/16	16/16	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	, ,(NR)	,(NR)
AEGL 2	,(0,37)	,(0.37)	,(,30)	,(,19)	,(,093)
AEGL 3	,(1.1)	,(1.1)	,(0,90)	,(0,57)	,(0,28)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of data.

AEGL 1 Motion by: Benson **Second by:** Ripple
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/10/09

Chemical: FENAMIPHOS **CAS Reg. No.:** 22224-92-6

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: WOODALL **Staff Scientist:** RAYNER

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	A	A	A	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	Y	Y	Y		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	Y	Y	Y		Alan Woolf	Y	Y	Y	
					TALLY				
					PASS/ FAIL				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	~~(0.99)~~ 1.0	0.80, ~~(0.99)~~ 0.78	0.70, ~~(.66)~~	0.53, ~~(.50)~~	0.43, ~~(.40)~~
AEGL 3	,(3.0)	,(2.4)	~~(2.0)~~ 2.1	1.6, ~~(1.5)~~	1.3, ~~(1.4)~~
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

~~150~~ 11/3/09

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: Bernas **Second by:** Niemeier
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

NAC/AEGL Meeting 49: September 9-11, 2009

Appendix M

Chemical: AUTOMOTIVE GASOLINE (UNLEADED) **CAS Reg. No.:** 86290-81-5 8006-61-9

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y				John Hinz	Y			
Marc Baril	Y				Jim Holler	Y			
Lynn Beasley	Y				Clarion Johnson	A			
Alan Becker	Y				Glenn Leach	A			
Robert Benson	Y				Richard Niemeier	Y			
Edward Bernas	Y				Mattias Oberg	Y			
Iris Camacho	A				Susan Ripple	Y			
George Cushmac	Y				George Rusch, Chair	Y			
Richard Erickson	Y				Daniel Sudakin	A			
Neeraja Erraguntla	Y				Marcel vanRaaij	Y			
David Freshwater	Y				George Woodall	Y			
Ralph Gingell	Y				Alan Woolf	Y			
					TALLY	20/20	20/20	20/20	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(730)	,(730)	,(730)	,(730)	,(730)
AEGL 2	*,(7500)	*(7500)	*,(7500)	*,(7500)	*,(7500)
AEGL 3	,(ND)	,(ND)	,(ND)	,(ND)	,(ND)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account. AEGL-2 IS HIGHER THAN ½ the LOWER EXPLOSIVE LIMIT (LEL = 62,000 mg/m³)

** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

ND = NOT DETERMINED UNDER NORMAL EXPOSURE SCENARIOS

NR= Not Recommended due to_____

AEGL 1 **Motion by:** Anderson **Second by:** Benson

AEGL 2 **Motion by:** " **Second by:** "

AEGL 3 **Motion by:** " **Second by:** "

LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/11/09

Appendix N

Chemical: CADMIUM **CAS Reg. No.:** 7440-43-9

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: RIPPLE **Staff Scientist:** RAYNER

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	Y	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	Y	Y	Y		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	A	A	A		Mattias Oberg	Y	Y	Y	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	A	A	A		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	Y	Y	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	A	A	A		Alan Woolf	Y	Y	Y	
					TALLY	17/17	17/17	17/17	
					PASS/ FAIL	P	P	P	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.13)	,(0.13)	,(0.10)	,(0.063)	,(0.041)
AEGL 2	,(1.4)	,(0.96)	,(0.96)	,(0.40)	,(0.20)
AEGL 3	,(8.5)	,(5.9)	,(4.7)	,(1.9)	,(0.93)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1 Motion by: Benson **Second by:** Hinz
AEGL 2 Motion by: Van Raaij **Second by:** Benson
AEGL 3 Motion by: Baril **Second by:** Benson
LOA Motion by: _____ **Second by:** _____

Chemical: RED PHOSPHORUS **CAS Reg. No.:** 7723-14-0

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: LEACH **Staff Scientist:** YOUNG

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		John Hinz	Y	Y	Y	
Marc Baril	P	Y	Y		Jim Holler	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Clarion Johnson	A	A	A	
Alan Becker	A	A	A		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Edward Bernas	P	P	P		Mattias Oberg	P	Y	P	
Iris Camacho	A	A	A		Susan Ripple	Y	Y	Y	
George Cushmac	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Richard Erickson	Y	Y	Y		Daniel Sudakin	A	A	A	
Neeraja Erraguntla	Y	Y	Y		Marcel vanRaaij	N	N	Y	
David Freshwater	Y	Y	Y		George Woodall	Y	Y	Y	
Ralph Gingell	P	P	P		Alan Woolf	Y	Y	Y	
					TALLY	14/15	16/17	16/16	
					PASS/ FAIL	P	P	P	

PPM, (mg/m³)	10 Min	30 Min PSV	1 Hr	4 Hr	8 Hr
AEGL 1	67 ([redacted])	4.6, 4.7 ([redacted])	3.7 , ([redacted])	0.93 , ([redacted])	0.47 ([redacted])
AEGL 2	, (20)	, (14)	, (11)	, (2.8)	, (1.4)
AEGL 3	, (85)	, (59)	, (47)	, (12)	, (5.9)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to ~~Lack of Data~~ ok

AEGL 1 Motion by: Bonam **Second by:** Hinz
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____